#14

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re. U.S. Patent No.: 4,467,807
Issued: August 28, 1984
To: Gene A. Bornzin
For: "RATE ADAPTIVE DEMAND PACEMAKER"

LETTER OF TRANSMITTAL OF APPLICATION
FOR EXTENSION OF PATENT TERM

Commissioner of Patents and Trademarks
United States Patent and Trademark Office
Washington, DC 20231

Sir:

Transmitted herewith for filing is an Application for Extension of Patent Term of U.S. Patent No. 4,467,807, and a duplicate application certified as such.

Please charge the filing fee of $750.00 to Deposit Account No. 13-2545 in the name of Medtronic, Inc. The Commissioner is hereby authorized to charge any additional fees which may be required or to credit any overpayment to Deposit Account No. 13-2545.

The Application transmitted herewith has been executed by the owner of the subject patent. Therefore, the present Application is complete and entitled to a filing date of July 11, 1986 as indicated by the Certificate of Mailing.

Respectfully submitted,

MEDTRONIC, INC.,

By: Robert C. Beck

Robert C. Beck
Reg. No. 28,184
(612) 574-3337

7000 Central Avenue N.E.
Minneapolis, MN 55432
Dated: July 11, 1986

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re. U.S. Patent No.: 4,467,807
Issued: August 28, 1984
To: Gene A. Bornzin
For: "RATE ADAPTIVE DEMAND PACEMAKER"

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. §156

Commissioner of Patents and Trademarks
United States Patent and Trademark Office
Washington, DC 20231

Sir:

Applicant, Medtronic, Inc., requests an extension of patent term of U.S. Letters Patent No. 4,467,807 pursuant to 35 USC 156. Further, Applicant represents that it is the assignee of the entire interest in and to U.S. Letters Patent No. 4,467,807, granted to Gene A. Bornzin by virtue of an Assignment recorded November 23, 1981, Reel 3955, Frame 132.

In support of this application, the applicant provides the information required by the Guidelines published by the U.S. Patent and Trademark Office. For the convenience of the Office, the information is supplied in the order specified by Section D(b) of the initial Guidelines:

(1) The approved product is the Activitrax Rate Responsive Pacemaker manufactured by Medtronic, Inc. which bears the Model Numbers 2447/2448 and 8400/8403/8402. The device is described in both the Technical Manual attached as Exhibit "A" and the Summary of Safety and Effectiveness attached as Exhibit "B". The pacemaker is a demand heart pacemaker for providing stimulating pulses to the heart at a predetermined rate in the absence of naturally occurring heartbeats. The device includes a sense amplifier for sensing naturally occurring heartbeats and for generating a reset signal in response thereto. There is also a pulse generator for generating stimulating pulses at a minimum

pacing rate, and which includes a timing means for providing each stimulating pulse separated by an escape interval corresponding to the pacing rate. The pulse generator further includes reset means responsive to a reset signal for resetting the timing means and restarting the escape interval. There is also included means for measuring a physiologic activity parameter indicative of the level of cardiac output demanded by the patient's body and for providing an escape interval modifying signal and means responsive to the escape interval modifying signal for adjusting the escape interval to provide pacing pulses on demand at a minimum rate correlated to the cardiac output requirements of the patient.

(2) The approved product was subject to a regulatory review under section 515(b) of the Federal Food, Drug and Cosmetic Act 21 USC 335. The pertinent regulations respecting such regulatory review are contained in 21 USC §§812, 820 et seq.; 860 et seq.; and 870 et seq.

(3) The Applicant received permission for commercial marketing of the approved product under §515 of the FFDCA on June 10, 1986.

(4) This application is being submitted within the sixty day period permitted under 35 USC §156, said period expiring on August 8, 1986.

(5) The patent for which extension is sought is identified as follows:

U.S. Patent No.: 4,467,807
Inventor: Gene A. Bornzin
Title: "RATE ADAPTIVE DEMAND PACEMAKER"
Application No.: 323,507
Filed: November 23, 1981
Date of Patent: August 28, 1984

(6) Attached hereto as Exhibit "C" is a complete copy of the patent identified in paragraph (5) above. Exhibit "D" is a cut-up copy of the patent with only a single column of the printed patent securely mounted on one side of a separate sheet.

(7) No disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate has been issued with respect to U.S. Patent 4,467,807.

(8) U.S. Patent 4,467,807 claims the approved product. Claims 1, 2, 5 and 6 read upon the approved product as follows:

Claim 1

The approved device is a demand heart pacemaker providing stimulating pulses to the heart at a predetermined rate in the absence of naturally occurring heartbeats. The approved device has a sense amplifier which comprises sensing means for sensing naturally occurring heart signals and for generating a reset signal. The pulse generator portion of the approved device generates stimulating pulses at a minimum pacing rate and achieves this result through a timing circuit which sets the escape interval corresponding to the pacing rate desired. Upon the occurrence of a reset signal generated by the sense amplifier, the timing circuitry is both reset and restarted beginning a new escape interval. The approved device further contains means for measuring a physiologic parameter which, in the instance of the approved device, is the physical activity level of the patient, and produces an escape interval modifying signal. This signal is coupled through circuitry which is responsive to the escape interval modifying signal which adjusts the escape interval of the pacemaker providing pacing pulses on

demand at a minimum rate correlated to the cardiac output requirements of the patient.

Claim 2 (Dependent on Claim 1)

The approved device includes circuitry which permits a reduction in the pacing rate if the activity level of the patient decreases, thus providing means for decreasing the escape interval of the device.

Claim 5 (Dependent on Claim 1)

The approved device also permits the increase in the escape interval of the patient in the absence of sensed physical activity of the patient, thus providing means for increasing the escape interval. The approved device may use the R-wave of the patient as detected by a lead implanted in the ventricle of the patient for establishing the predetermined electrical event which generates the reset signal.

Claim 6 (Dependent on Claim 1)

The approved device may be coupled to a lead implanted in the atrium of the patient so that the P-wave of the patient's heartbeat generates the reset signal called for by this claim.

(9) On November 17, 1983, a clinical investigation on humans involving the Activitrax pacing system was begun as noted in Exhibit "E". The latter date establishes the beginning of the "regulatory review period" under 35 USC 156(g)(3) as November 17, 1983, the date a clinical investigation on humans involving the device was begun.

On August 3, 1983, Medtronic, the assignor of U.S. Patent No. 4,467,807, submitted to the FDA a IDE entitled "IDE Application For Medtronic Model 2447/2448 Pulse Generators" under section 520(g) of the FFDCA to permit the interstate shipment of

the Activitrax device for the purpose of conducting clinical studies to support the subsequent premarket approval application (PMAA) for the Activitrax pacing system. A copy of the letter transmitting the IDE to the FDA is attached as Exhibit "F". By letter dated November 17, 1983, the FDA acknowledged receipt of the IDE assigning the IDE No. G830107/A1, and indicated that the IDE had been approved. A copy of this letter has been attached as Exhibit "E".

Medtronic submitted a PMAA under section 515 of FFDCA for the Activitrax pacing system. A copy of the cover letter and associated correspondence is attached as Exhibit "G". This letter was received by the FDA on July 19, 1985. A copy of the subsequent approval letter dated June 10, 1986 is attached as Exhibit "H".

Thus, for the purposes of the "regulatory review period" under 35 USC 156(g)(3), June 10, 1986, is the date of approval for the application for the Activitrax system effectively filed on August 3, 1983.

(10) A brief description of the activities undertaken by the Applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities is produced as Exhibit "I" which shows the activities involved.

(11) Section 156(a) provides, in relevant part, (a) that the term of the patent which claims a product shall be extended if the term of the patent has not expired before an application for extension is submitted, (b) the term of the patent has never been extended, (c) the application for extension is submitted by the owner of record of the patent in accordance with 35 USC 156(d), (d) the product has been subject to a regulatory review period before its commercial marketing or use, and (e) the permission for the commercial marketing or use of the product after such a

regulatory review period is the first permitted commercial marketing of the device.

As described below by corresponding numeral, each of these elements is satisfied herein:

(a) The term of U.S. Patent No. 4,467,807 ends August 28, 2001, thus the application has been submitted before the expiration date of the patent term.

(b) The term of this patent has never been extended.

(c) The application is submitted by Medtronic, the assignee of record of the application.

(d) As evidence by the November 17, 1983 letter from the FDA, Exhibit "E", the product was subject to a regulatory review period under section 515 of the FFDCA before its commercial marketing or use.

(e) Finally, the permission for commercial marketing of the Activitrax pacing system after regulatory review under section 515 is the first permitted commercial marketing of the claimed device which is confirmed by the absence of any approved PMAA for the device prior to the date of June 10, 1986.

(f) The subject patent, U.S. 4,467,807, issued on August 28, 1984.

Therefore, the term of U.S. Patent No. 4,467,807 should be extended by 652 days to June 15, 2003. This extension was determined on the following basis:

As set forth in 35 USC 156(g)(3), the regulatory review period equals the length of time between when a clinical investigation on humans was begun (November 17, 1983), and the effective submission of the PMAA (June 10, 1986), which is a period of 937 days.

Pursuant to 35 USC 156(c), the term of the patent elligible for extension shall be extended by the time equal to the

regulatory review period which occurs after the date the patent issued. In this case, the patent isssued after the clinical investigations had begun.

(12) The Applicant hereby acknowledges its duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations made relative to this application for patent term extension.

(13) The prescribed fee of $750.00 for receiving and acting upon this application is enclosed herewith along with an authorization to charge Deposit Account No. 13-2545 for any deficiency.

DECLARATION

The undersigned attorney for Applicant declares that he is authorized to execute this application on behalf of Applicant, pursuant to a Power of Attorney submitted herewith;

That he has reviewed and understands the contents of this application for extension of patent term of U.S. Patent No. 4,467,807;

That he believes the patent is subject to an extension pursuant to Section A of the Guidelines;

That he believes an extension of the length claimed is fully justified under 35 USC §156; and

That he believes the patent for which the extension is sought meets the conditions for the extension of the term of the patent as set forth in Section B of the Guidelines.

The undersigned hereby declares further that all statements made herein of his own knowledge are true and that all statements made upon information and belief are believed to be true; and further that these statements were made with the knowledge that

willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Tile 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

Respectfully submitted,

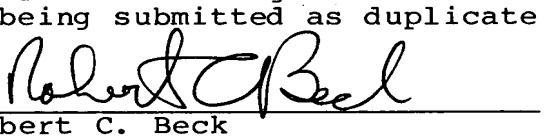
MEDTRONIC, INC.,

By: 
Robert C. Beck
Reg. No. 28,184
(612) 574-3337

7000 Central Avenue N.E.
Minneapolis, MN 55432
Date: July 11, 1986

CERTIFICATE OF MAILING

The undersigned hereby certifies that this Application for Extension of Patent Term under 35 USC §156 including its attachments and supporting papers is being submitted as duplicate originals.


Robert C. Beck

Date: July 11, 1986

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re. U.S. Patent No.: 4,467,807
Issued: August 28, 1984
To: Gene A. Bornzin
For: "RATE ADAPTIVE DEMAND PACEMAKER"

POWER OF ATTORNEY

The undersigned applicant hereby appoints:

Robert C. Beck
MEDTRONIC, INC.
7000 central Avenue N.E.
Minneapolis, MN 55432
(612) 574-3337

as its attorney to execute the above-identified application to extend the term of U.S. Patent No. 4,467,807 on its behalf, and to transact all business in the Patent and Trademark Office connected therewith. Please continue to recognize all other previously appointed attorneys.

Respectfully submitted,

MEDTRONIC, INC.,

By: William E. Drake
William E. Drake
Deputy General Counsel
and Assistant Secretary

Dated: July 11, 1986

EXHIBIT B

Summary of Safety and Effectiveness Data for the Medtronic® Activitrax™ Models 8400, 8402, and 8403 Pulse Generator and the Model 9710 Programmer with the Model 9725 MemoryMod™ Program Module

Summary of Safety and Effectiveness Data

I. General Information

Device Generic Name:	Implantable Pulse Generator and Programmer
Device Trade Name:	Activitrax™ Models 8400, 8402, and 8403 Pulse Generator and Model 9710 Programmer with the Model 9725 MemoryMod™ Program Module
Applicant's Name and Address:	Medtronic, Inc. 7000 Central Avenue N.E. Minneapolis, MN 55432
Pre-Market Approval (PMA) Application Number:	P850051
Date of Panel Recommendation:	April 21, 1986
Date of Notice of Approval to the Applicant:	

II. Indications for Use

The single chamber Activitrax™ Models 8400, 8402, and 8403 Pulse Generator and Model 9710 Programmer with the Model 9725 MemoryMod™ Program Module are indicated where permanent ventricular or atrial (Models 8400, and 8402 only) pacing is used for patients who may benefit from pacing rate variability associated with the level of physical activity. Ventricular indications include atrial flutter or fibrillation with slow ventricular response; sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, or bradycardia-tachycardia syndrome); or A-V (atrioventricular) block. Atrial indications for the bipolar Models 8400 and 8402 include sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, or bradycardia-tachycardia syndrome). Asynchronous pacing (VOO/AOO or VOO/AOO + activity) is contraindicated in the presence of intrinsic rhythm and may be contraindicated if intrinsic rhythm is likely to occur. Atrial pacing is contraindicated in the presence of an A-V conduction disturbance. While atrial use is limited to patients with intact A-V conduction, one way that atrial performance differs from ventricular performance is that it may be affected by sensing of the R-wave on the atrial lead. Atrial use of the unipolar Model 8403 is contraindicated for this reason, and the labeling cautions about the atrial use of the bipolar Models 8400 and 8402.

III. Device Description

The Activitrax™ Models 8400, 8402, and 8403 Pulse Generator are single chamber, multi-mode, programmable pulse generators which sense and respond to the patient's activity. The pacing system consists of the Activitrax™ Pulse Generator, a commercially available pacemaker lead and the Model 9710 Pacemaker Programmer with the Model 9725 MemoryMod™ Program Module.

The Model 8400 is a bipolar pulse generator with a low profile connector; the Model 8402 is a bipolar pulse generator with a standard bipolar connector; and the Model 8403 is a unipolar pulse generator with a unipolar connector. The pulse generators are powered by a hermetically sealed lithium-iodine battery and use hermetically sealed integrated circuits.

The device's activity sensor is a piezoceramic sensor mounted on the inner surface of the hermetically sealed pacemaker can. Normal patient activity causes slight deflections in the pacemaker can which produces piezoelectric signals which are processed by the activity sensing circuitry to modify the pacing rate.

The programmable activity pacing functions are: the Basic Rate, the Maximum Activity Rate, Activity Threshold, and Rate Response. Mode, sensitivity, pulse width, pulse amplitude, and hysteresis rate are programmable. The pacemaker is designed for permanent pacing in any one of the following modes: demand (VVI/AAI), asynchronous (VOO/AOO), demand + activity, and asynchronous + activity.

The need to more closely monitor the patient is signaled when a 20% increase is observed between the measured pulse width and the programmed value. Based upon simulated studies, the applicant estimates that approximately nine months (seven months minimum) elapse between the occurrence of a 20% increase in pulse width and the elective replacement indication when programmed to 5.0 volts (V), 0.5 milliseconds (ms), 70 pulses per minute (ppm) with 100% pacing into a 500 ohm (Ω) load. The elective replacement indication consists of a change to the demand mode of pacing at a rate of 65ppm. The applicant estimates that approximately three months of service life (two months minimum) remain after the onset of the indicator, assuming programmed values of 5.0V, 0.5ms and 100% pacing into a 500Ω load. During this time the pacemaker's mode, rate or hysteresis functions cannot be reprogrammed.

IV. Alternative Practices and Procedures

Cardiac pacing is the accepted treatment for the indications described in Section II above. Other commercially available systems, single or dual chamber, may meet the needs of the patients with the symptoms described in Section II above. This is the first approved PMA for a single chamber, rate responsive pacemaker system.

V. Potential Adverse Effects of the Device on Health

Potential adverse effects associated with all pacemaker systems include: loss of normal pacemaker function due to battery failure or other component failure; inability to reprogram a pacemaker pulse generator because of programmer failure; infection; erosion; undesired muscle or nerve stimulation; and inadequate sensing or pacing. Any demand pulse generator can be affected by magnetic, electrical, and electromagnetic signals of sufficient strength or with characteristics which mimic cardiac function. Possible effects of electrical interference on pulse generator operation include reversion to asynchronous pacing, inhibition of output pulses and rapid synchronous pacing. Certain environmental sources can couple sufficient energy into a cardiac pacing system to damage the pulse generator or cardiac tissue adjacent to the electrodes.

Potential adverse effects associated with activity pacing include loss of activity detection due to activity sensor failure which would result in fixed rate (VVI) pacing. There is also a potential for rises in the pacing rate from inappropriate detections of muscle stimulation, external pressure applied to the pacemaker, or external mechanical stimulation of the pulse generator.

Failure of the pulse generator system to function properly may result in the patient experiencing the symptoms for which the pulse generator was originally indicated.

VI. Summary of Studies

A. Component Tests

Electronic and mechanical components are design verified in accordance with the applicant's specifications. Twenty-two hybrid electronic modules underwent 1,000 hour accelerated life testing at a temperature of 100 degrees Centigrade (°C). Eighty-one different electrical tests were performed on each hybrid in accordance

with applicable sections of the appropriate military testing standard (MIL-STD-883). All hybrid electronic modules passed the tests.

Seventy-eight samples of the digital programmable controller integrated circuit (IC), seventy-six samples of the amplifier IC and twenty-two activity sensing ICs were subjected to a 1,000 hour accelerated life test at 125°C. Functional electrical tests were performed on each IC before and after the accelerated life test. The ICs passed all tests demonstrating that function and parameter stability were not affected by the accelerated life test.

A sample of 22 digital programmable controller ICs, 22 activity sensing ICs and 76 amplifier ICs were subjected to environmental testing. The samples were subjected to temperature cycling of -65° to 150°C followed by constant acceleration testing at 10,000 to 30,000 times the force of gravity (g). The units were electrically tested before and after the environmental stresses. All ICs demonstrated function and parameter stability throughout the environmental testing.

The lithium-iodine battery was subjected to a series of mechanical and thermal stress tests (8 cells), accelerated discharge tests (64 cells), and visual inspections. The results of these tests showed performance consistent with high reliability pacemaker requirements.

Four activity sensor assemblies (mounted on the pulse generator can) were subjected to an alternating series of three environmental tests (mechanical and thermal stresses) and two life tests (70°C for 168 hours). There were no failures observed during the test and no significant shifts in measured parameters.

Twenty-five connector (header) assemblies from the Models 8400, 8402, and 8403 with attached leads were tested for electrical leakage by impedance measurements and performed within the applicant's specifications which are consistent with high reliability pacemaker requirements.

B. Device Tests

Environmental stress testing consisting of temperature storage (-18°C to 55°C for 6 hours each), mechanical vibration (5 to 500 hertz at 2.5 times the force of gravity (g)), mechanical shock (600g) was performed on two Model 8400 and three Model 8403 pulse generators. All device parameters remained within the applicant's labeled specifications. The Models 8400 and 8402 are bipolar devices and differ only in connector design.

In the following tests, testing of the Model 8400 only is sufficient for the Models 8400 and 8402.

Two Model 8400 and three Model 8403 pulse generators were tested to determine their susceptibility to electromagnetic interference according to the August 1975 draft standards of the American Association for Medical Instrumentation (AAMI). The results of these tests indicated that the generators were within the AAMI requirements for radiated interference and were not significantly affected by electromagnetic interference.

Two Model 8400 and three Model 8403 pulse generators were subjected to three 400 watt-second (stored) defibrillation pulses of each polarity in vitro. All devices demonstrated no change in the pre- and post-test electrical output parameters.

Two Model 8400 and three Model 8403 pulse generators were subjected to three modes of electrosurgical currents in vitro. After the electrosurgical currents were removed, three test devices returned to power-on conditions (VVI mode, 922ms pulse period). These conditions are reprogrammable with a Medtronic Model 9710 Programmer with a Model 9725 MemcryMod™ Program Module. Two devices lost output in response to the electrosurgical currents. Failure analysis showed that devices with depleted batteries are susceptible to failure but those with new batteries are not. This is described in the labeling as a warning.

One Model 8400 and one Model 8403 pulse generator were tested to determine the susceptibility of the pulse generators to external acoustic vibrations. No pacemaker rate change was observed at levels below 112 decibels.

The effects of simulated muscle stimulation was evaluated on the activity pacing rate of three unipolar Model 8403 pulse generators. At the highest programmable rate response, the activity pacing rate stabilized at approximately 100ppm in response to simulated muscle stimulation and the devices responded normally to additional stimulation.

Externalized testing was performed by strapping devices (two Model 8400, two Model 8403) onto an individual's chest while performing different levels of activity. The monitored activity pacing rates were similar for the bipolar and unipolar models. Activity pacing rate changes during and after exercise were evaluated on 6 normal subjects and were found to be similar to the subject's sinus rate changes.

Testing was performed to determine the activity pacing rate response curves for three different programmed rate response values (1, 5, 10) on 46 Activitrax™ pulse generators. Testing was also performed to determine threshold values (low, medium and high) as a function of the amplitude of the sensed activity on 53 Activitrax™ pulse generators. These tests indicate that the rate response curves and threshold values met the applicant's designed specification.

Fifteen Activitrax™ pulse generators were tested to determine the time required for the devices to respond to a sensed activity and increase the pacing rate and the time required for the devices to respond when the activity ceases and decrease the pacing rate. The results met the applicant's specification which approximates the physiological response in normal patients.

Biocompatibility

The polyurethane, silicone rubber and titanium used in the Activitrax™ Models 8400, 8402, and 8403 passed all USP XXI pyrogen, USP XXI (Class V) biological tests for plastics, and USP XXI intramuscular implant tests. The materials also passed the Ames mutagenicity assay, hemolysis and tissue culture tests. The results of these tests show that the materials used in the pulse generators are non-pyrogenic, non-toxic, biocompatible, non-mutagenic, non-hemolytic and inert.

C. Programmer Testing

A series of environmental, functional and software tests were performed to check the programming effectiveness. Test results indicated the programmer performed according to the applicant's specifications which are consistent with the labeling.

D. Animal Studies

An acute study was performed in one canine to evaluate the effects of muscle stimulation on the unipolar Model 8403 pulse generator's activity pacing rate. One device was modified to ensure that muscle stimulation would occur. With the rate response programmed to the most responsive setting, the pacing rate stabilized at 96 ppm with muscle stimulation, which verified the results of the *in vitro* simulation.

E. Clinical Studies

The objectives of the Activitrax™ clinical study were to confirm the proper operation, safety, and effectiveness of the Activitrax™ pulse generator in providing

rate-responsive pacing vs. fixed rate demand pacing.

The clinical study on the present Activitrax™ configurations began in May 1984, and data were collected at implant and post-implant on 222 patients by 61 investigators worldwide as of October 15, 1985. The mean age for the patients was 61 years with a range of 6 months to 93 years. Of the 222 implants, 186 were bipolar pulse generators and 36 were unipolar (Model 8403) pulse generators. Lead placement was in the ventricle in 206 implants and in the atrium for 16 implants.

The indications for the use of the Activitrax™ pulse generator in the study population were sinus bradycardia (43 cases), bradycardia-tachycardia syndrome (30 cases), sinus arrest (15 cases), atrial tachyarrhythmia (58 cases), and various degrees of A-V block (161 cases). These indications are not mutually exclusive.

The follow-up schedule for the study was pre-discharge from the hospital and 1, 3, 6, 12 and 18 months post-implant. There were 307 reprogrammings during follow-up to optimize device performance as required. Of the 222 implants, 143 were initially in the VVI/AAI + activity mode and 79 were in the VVI/AAI mode. At the last follow-up visit, 205 patients were in the VVI/AAI + activity mode and 17 patients were in the VVI/AAI mode. Of the 222 pulse generator implants, 154 were implanted for 4 months or longer and 68 were implanted for less than 4 months as of October 15, 1985. Of 546 scheduled follow-up visits, data was provided by the investigators for 477 or 87% of them.

In order to assess effectiveness of the Activitrax™ pulse generator, 120 patients underwent paired (i.e., tested in VVI/AAI mode and VVI/AAI + activity mode on the same day) exercise tolerance treadmill tests using a modified Naughton protocol usually at the 1 month follow-up. The results from these patients indicate a mean increase in the VVI/AAI + activity mode of 31.2% in maximal heart rate, a 36.8% increase in work capacity, and a 32.0% increase in exercise time, all of which are statistically significant (i.e., the probability that data from exercise tests in the VVI/AAI mode vs. the VVI/AAI + activity mode are the same is less than one in ten thousand ($p<.0001$)).

In a subgroup of 54 totally paced patients in the above 120 patient population, maximal heart rate showed an average percent increase of 57.7%, work capacity - 61.4%, and exercise time - 52.4%, all of which are statistically significant ($p<.0001$). For this subgroup of 54 patients, the percentage increase in heart rate, treadmill time, and work capacity can be attributed entirely to the

performance of the Activitrax™ pulse generator.

The remaining 67 patients in the above 120 patient population (one patient was tested twice and was qualified for inclusion in both subgroups) who exhibited some intrinsic rhythm during exercise showed an average percent increase of 9.9% in maximal heart rate, a 16.8% increase in work capacity and a 15.6% increase in exercise time, all of which are statistically significant. Therefore, patients who are intermittently paced by the device still derive benefit.

Throughout the above studies, exercise was voluntarily terminated by the patient due to fatigue or dyspnea and no adverse events, including dysrhythmias or angina, were reported during, or immediately after, the exercise studies.

While atrial use is limited to patients with intact A-V conduction, one way that atrial performance differs from ventricular performance is that it may be affected by sensing of the R-wave on the atrial lead. Atrial use of the unipolar Model 8403 is contraindicated for this reason, and the labeling cautions about the atrial use of the bipolar Models 8400 and 8402.

Unipolar Model 8403 pulse generator performance is consistent with that of the bipolar pulse generators except that unipolar pulse generators can cause muscle stimulation which can result in activity pacing rate increases. Muscle stimulation is an infrequent occurrence of all unipolar pulse generators.

Seventy-seven 24 hour Holter recordings, along with diaries, were obtained on selected patients. These recordings document basic rate pacing during the periods of sleep and appropriate changes in heart rate during daily activities and physical exertion. Sensing of environmental stimuli has been observed occasionally to cause increases in the pacing rate (e.g., in a car) which were generally not detected by the patient. None of these cases required reprogramming. There have been no instances in the Holter recordings indicating that the Activitrax™ pulse generators have failed to respond with pacing rate increases when called for by increased patient physical activity.

Analysis of ECGs collected during the clinical study confirmed four device-related pacing characteristics related to activity pacing. The first two are events noted on analysis of ECGs which were not perceived by the patients. The first is an occasional extra paced pulse observed in seven patients. The second is a rate variability and a limitation of the attainment of the

maximum programmed rate caused by oversensing on the implanted lead observed in twenty-two patients. The third involves increases in the pacing rate with external pressure applied to the pacemaker reported in two patients. The fourth concerns muscle stimulation by the device causing increases in the activity pacing rate clinically confirmed in two patients. All of these phenomena are confined to the activity mode of operation, deemed by investigators to be not clinically significant, and are addressed in the pacemaker labeling. An additional device related pacing characteristic was reported in one patient since the meeting of the Circulatory System Devices Panel on April 21, 1986. In the asynchronous + activity mode, an intrinsic R-wave was seen to have an effect similar to oversensing in that rate variability occurred as an interval extension. This could also limit the attainment of the maximum programmed rate. Because of concerns about competitive pacing, the labeling was changed to contraindicate this mode in the presence of intrinsic R-waves.

There were 15 complications reported during the study. Two (2) cases were reported where the device was reprogrammed out of the VVI/AAI + activity mode due to angina. In one case the device was subsequently programmed back to the activity mode at a decreased maximum activity rate. In the other case, the patient remains in the VVI mode. The remaining cases were lead related complications: loss of capture (4), loss of sensing (2), electrical oversensing (1), phrenic nerve stimulation (1), ventricular arrhythmia (1), thrombosis (1), hematoma (1), seroma (1) and infection (1). These lead related cases were corrected by lead replacement (5), lead repositioning (4), drugs (2), or no action (2). Seven patient deaths were reported during the study. In each case the investigator determined that the death was not pacemaker related. There were no device failures reported, and no unanticipated adverse device effects have been observed during the Activitrax™ study.

Of the 222 pulse generator implants, 154 were implanted for 4 months or longer and 68 were implanted for less than 4 months as of October 15, 1985. The number remaining implanted is 215, with no explants other than those occurring after patient death.

VII. Conclusions Drawn From Studies

The in vitro test results provide reasonable assurance that Activitrax™ is reliable and biocompatible. The in vitro, animal and clinical test results provide reasonable assurance that Activitrax™ performs as designed and is safe and effective when it is used as indicated in the labeling.

VIII. Panel Recommendations

The Circulatory System Devices Panel reviewed this application at a public meeting on April 21, 1986, and recommended approval of the Activitrax™ Pacemaker System.

IX. FDA Decision

On May 9, 1986, FDA completed an inspection of Medtronic Inc.'s manufacturing facilities and determined that the manufacturer was in compliance with the device Good Manufacturing Practice regulations. FDA concurred with the above recommendation of the Circulatory System Devices Panel with one change. The Panel did approve the use of the asynchronous + activity mode. Since the Panel meeting on April 21, 1986, FDA was apprised of an additional device related pacing characteristic with the asynchronous + activity mode (see Section VI) and the applicant changed the labeling to contraindicate the use of that mode and the use of the asynchronous (VOO/AOO) mode in the presence of competitive rhythms. FDA has determined that this labeling revision is adequate for the purposes of ensuring the safety and effectiveness of this device for its intended use.

FDA approved the PMA on . FDA approval is subject to the applicant's compliance with the standard "Conditions of Approval for Pulse Generators and Programmers" (Attachment A) and the condition that the sale, distribution and use of the device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(4) of the act.

X. Approval Specifications

The post-approval requirements are discussed above in Section IX above.

All approved labeling is available to interested persons for inspection at the Food and Drug Administration, Center for Devices and Radiological Health, Document Mail Center (HFZ-401), 8757 Georgia Avenue, Silver Spring, Maryland 20910.

EXHIBIT

United States Patent [19]

Bornzin

[11] **Patent Number: 4,467,807**

[45] **Date of Patent: Aug. 28, 1984**

[54] **RATE ADAPTIVE DEMAND PACEMAKER**

[75] Inventor: **Gene A. Bornzin, Coon Rapids, Minn.**

[73] Assignee: **Medtronic, Inc., Minneapolis, Minn.**

[21] Appl. No.: **323,507**

[22] Filed: **Nov. 23, 1981**

[51] Int. Cl.³ **A61N 1/36**
[52] U.S. Cl. ..... **128/419 PG**
[58] Field of Search ..... 128/419 PG

[56] References Cited

U.S. PATENT DOCUMENTS

3,648,707	3/1972	Greatbatch	128/419 PG
4,052,991	10/1977	Zacouto	128/419 PG
4,202,339	5/1980	Wirtzfeld et al.	128/419 PG
4,313,442	2/1982	Knudson	128/419

OTHER PUBLICATIONS

"Relation Between QT Interval and Heart Rate New Design of Physiologically Adaptive Cardiac Pacemaker" by A. F. Rickards et al., published Jan., 1981, edition of the British Heart Journal, vol. 45, pp. 56-61.

"Frequenzsteuerung von Schrittmachern durch Bluttemperatur" by Weisswange et al., published in the Journal Deutsch Gesellschaft Fuer Kreislaufforschung, vol. 44, 1978.

Abstract entitled "An 'On Demand Pacemaker' Responsive to Respiration Rate" by Ionescu, Dept. of Cell Biology, BioMedical Engineering Unit, Institute of Biological Sciences, Splaiul Independentei 296, R-767-48-Bucharest, Rumania.

Article entitled "Ein Herzschrittmacher mit Belastungsabhangiger Frequenzregulation" by H. D. Funke, published in Biomedizinische Technik, Band 20, Heft 6/1975.

Abstract "Results, Problems and Perspectives in the Autoregulating Pacemaker" by Cammilli et al., published in the May-Jun. 1980 edition of Pace Magazine.

Article entitled "A Physiologically Controlled Cardiac Pacemaker" by J. L. Krasner et al., published in the Journal of the American Association for Medical Instrumentation, vol. 1, No. 3, Nov./Dec. 1966.

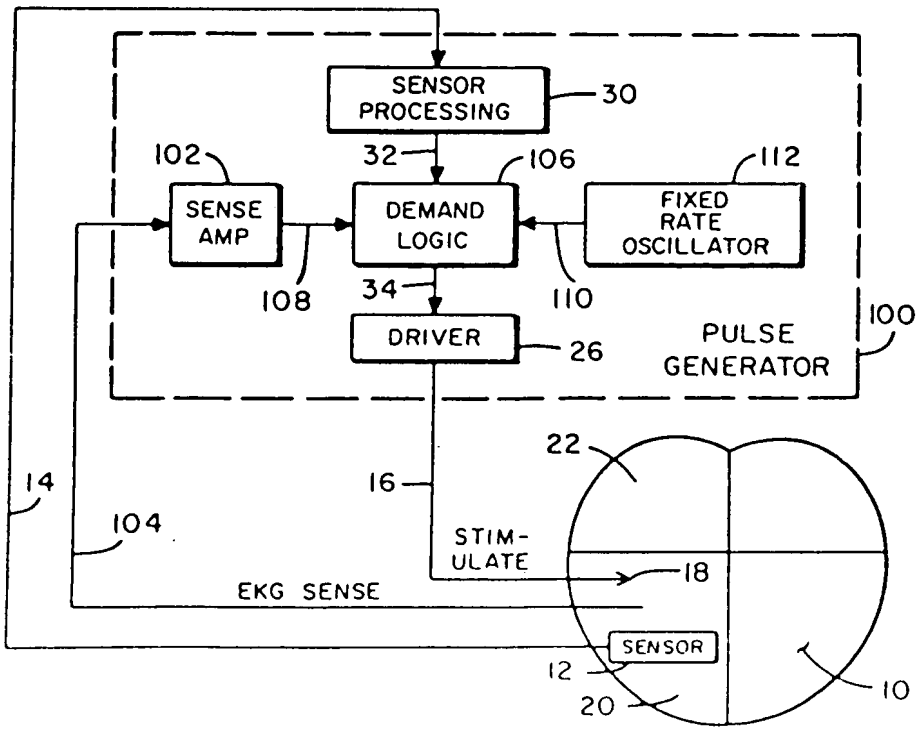
An article entitled "A New Pacemaker Autoregulating the Rate of Pacing in Relation to Metabolic Needs," by Cammilli, et al., published in the Proceedings of the 5th International Symposium, 1976 Tokyo.

Primary Examiner—William E. Kamm
Attorney, Agent, or Firm—Reed A. Duthler; John L. Rooney; Joseph F. Breimayer

[57] ABSTRACT

An implantable pacer having an effective stimulation rate which varies in response to a measured physiological parameter. Changes in the parameter to be measured must be related to physiologically required changes in heart rate. The level of oxygen within intracardiac or pulmonary artery venous blood is the preferred parameter. This parameter is measured by an oxygen sensor located on a transvenously implanted lead. As with normal demand pacers, a sensing electrode, also located on the lead, provides the pacer with an indication of whether a pacing pulse must be generated. The measured physiological parameter determines the escape interval for demand pacing. As such, a given minimum rate is determined for a given level of molecular oxygen in the intracardiac or pulmonary artery venous blood. The technique is readily employed in both ventricular and atrial-ventricular sequential modes.

7 Claims, 7 Drawing Figures



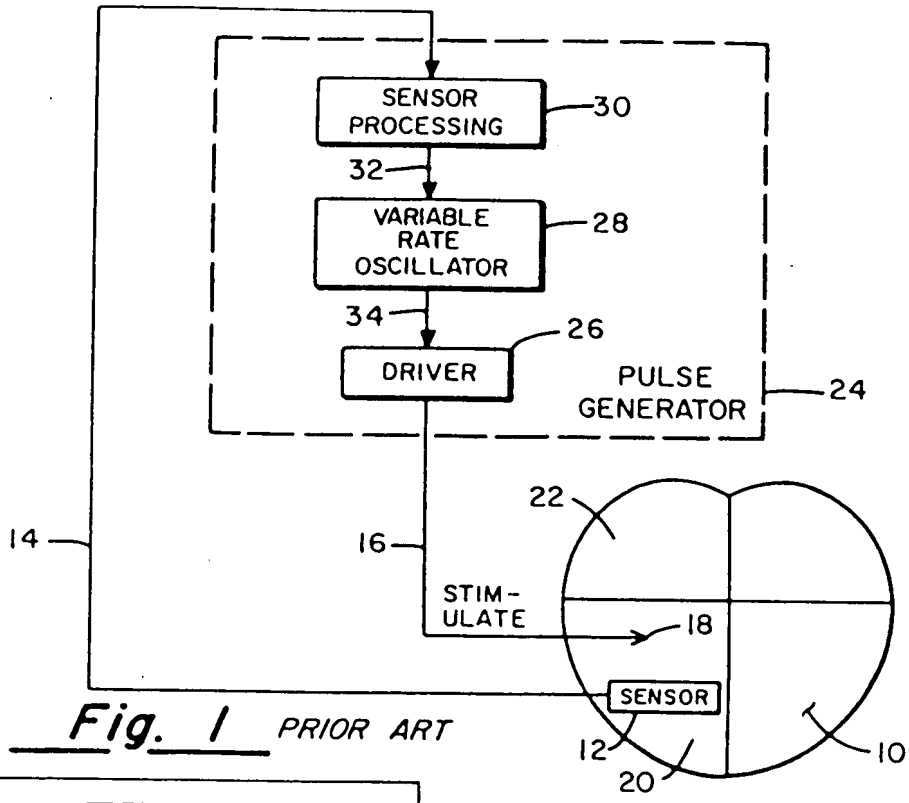


Fig. 1 PRIOR ART

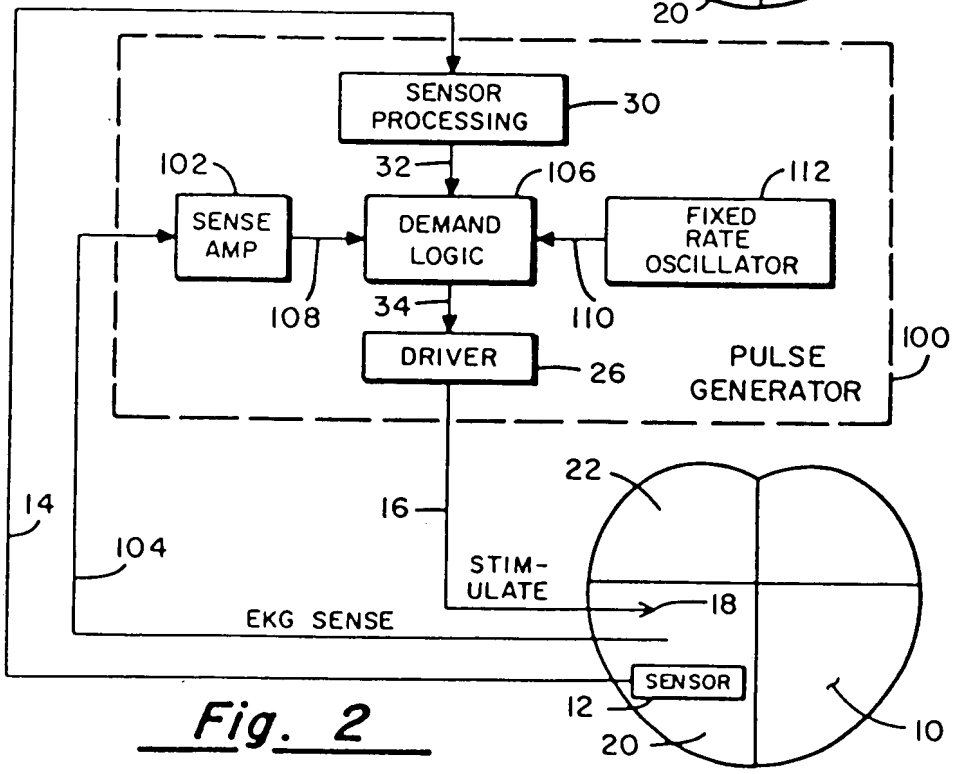


Fig. 2

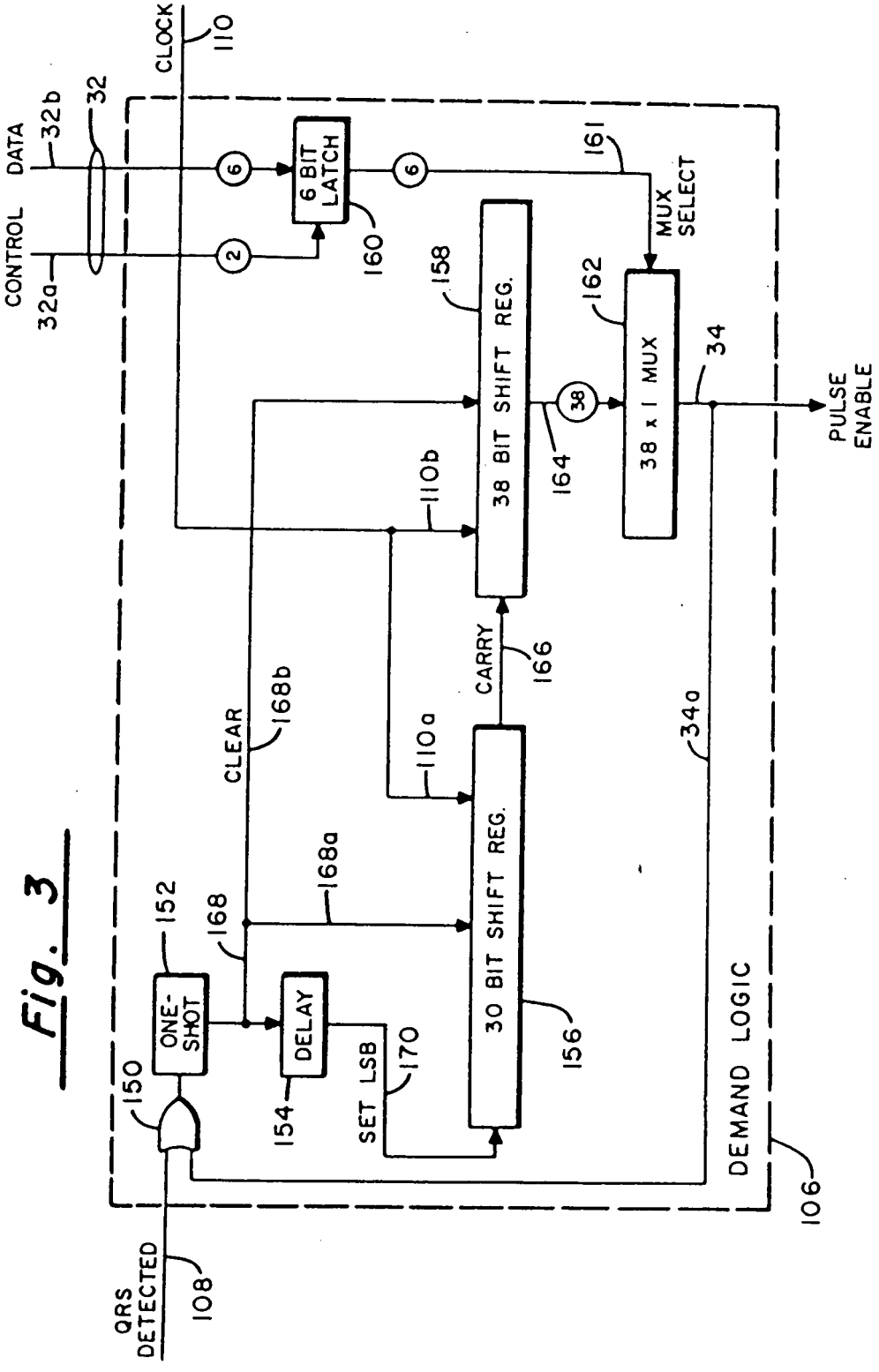
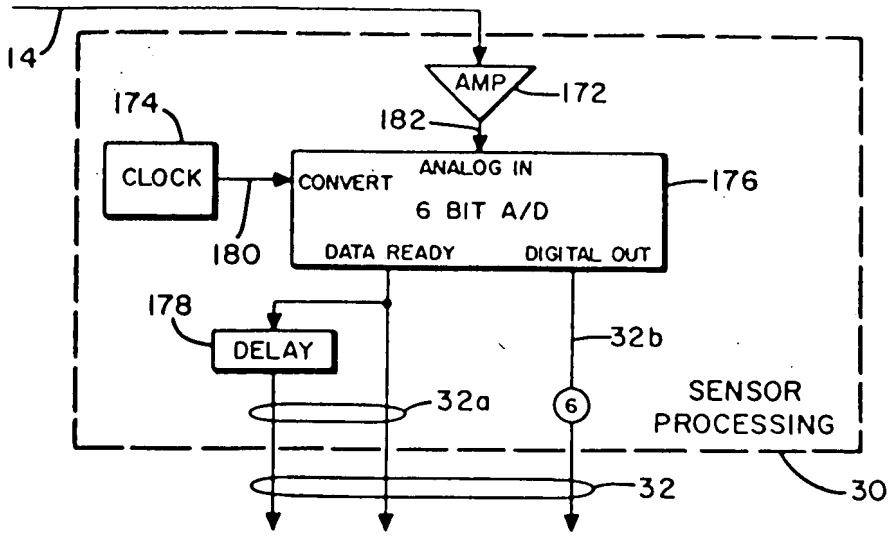

CLOCK
110
DATA
32b
32
CONTROL
32a
6
2
6 BIT LATCH
160
6
161
MUX SELECT
158
38 BIT SHIFT REG.
162
38 x 1 MUX
34
PULSE ENABLE
38
164
110b
CARRY
166
CLEAR
168b
110a
34a
168a
168
152
ONE-SHOT
DELAY
154
SET LSB
170
30 BIT SHIFT REG.
156
150
DEMAND LOGIC
106
QRS DETECTED
108

Fig. 3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AMP
172
174
182
CLOCK
CONVERT
ANALOG IN
6 BIT A/D
176
180
DATA READY
DIGITAL OUT
178
DELAY
32b
32a
6
SENSOR
PROCESSING
32
30

Fig. 4

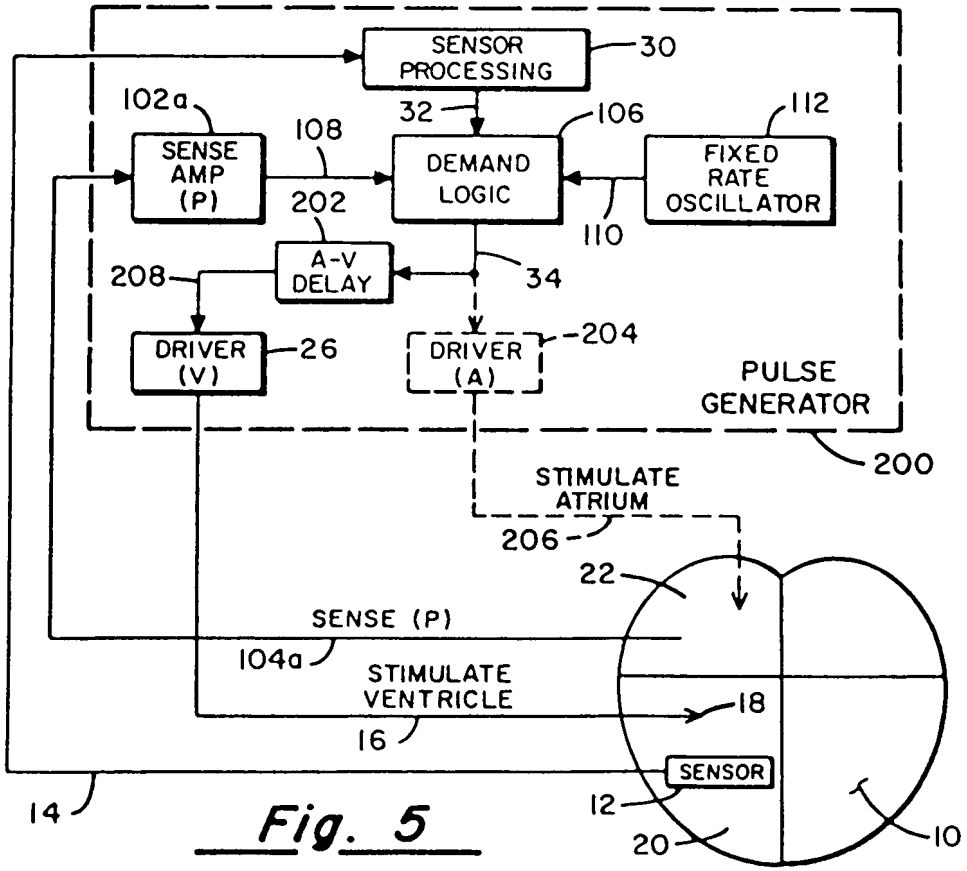
SENSOR
PROCESSING
30
102a
32
106
112
108
SENSE
AMP
(P)
DEMAND
LOGIC
FIXED
RATE
OSCILLATOR
202
110
A-V
DELAY
208
34
DRIVER
(V)
26
DRIVER
(A)
204
PULSE
GENERATOR
200
STIMULATE
ATRIUM
206
22
SENSE (P)
104a
STIMULATE
VENTRICLE
18
16
SENSOR
14
12
20
10

Fig. 5

BIT POSITION	RATE (BPM)
30	120
36	100
40	90
45	80
50	72
55	65.4
60	60
65	55.4
70	51.4
75	48
78	46

Fig. 6a

O_2 LEVEL (%)	BIT POSITION	6 BIT LATCH MSB LSB
70+	67	1 0 0 0 0 1
70	60	0 1 1 1 1 0
68	50	0 1 0 1 0 0
66	45	0 0 1 1 1 1
64	40	0 0 1 0 1 0
62	36	0 0 0 1 1 0
60	30	0 0 0 0 0 0

Fig. 6b

RATE ADAPTIVE DEMAND PACEMAKER

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to medical devices, and more specifically relates to implantable electronic devices for muscle stimulation.

2. Description of the Prior Art

The earliest implantable pacing systems operate asynchronously to normal physiologic functions. U.S. Pat. No. 3,057,356, issued to Greatbatch, teaches such a pacer which has a fixed rate oscillator coupled to an output driver circuit. Each cycle of the fixed rate oscillator causes generation of a stimulating pulse by the output driver circuit. Designs soon incorporated the demand feature which senses natural electrical activity in the heart and generates a stimulating pulse only if none is provided physiologically within a fixed escapement period. Demand mode pacers are now the most popular and probably outnumber all other types combined. Even though later improvements provide programmability of the escape interval, the effective pacing rate of such demand pacers is non-responsive to changes in physiological requirements.

There has been considerable work done in the area of physiologically controlled pacers. Most of these devices measure some parameter and adjust the period of the oscillator in response to changes therein. An early such device is taught by Cohen in U.S. Pat. No. 3,358,690. In this special case, however, the physiologic parameter measured is instantaneous blood pressure within the right atrium. This system will apparently work well for patients having complete atrial ventricular block with properly paced atria. The Cohen approach is not likely to be effective for sick sinus syndrome, sinus/atrial block, or similar disorders.

Later physiologically controlled pacer systems have been developed which have more general application and may be categorized by the parameter measured. Krasner et al. in U.S. Pat. No. 3,593,718 teaches sensing of mechanical activity within the thorax. It is assumed that changes in respiration rate are thereby sensed. The oscillator of the pacing system has its rate controlled by changes in this parameter. Dahl, in U.S. Pat. No. 4,140,132 teaches an improved implantable sensor for determining level of a patient's physical activity for rate-controlling a pacer as taught by Krasner et al.

Bozal Gonzalez in U.S. Pat. No. 4,201,219 teaches rate control of a pacer based upon neurological activity. Electrodes imbedded in the nervous system sense electrical activity. Somehow, the amount of this electrical activity is used to control the oscillator rate of an asynchronous pacer.

By far the most promising techniques appear to involve the sensing of certain chemical parameters of venous, often intracardiac blood. Alcidi in U.S. Pat. No. 4,009,721 teaches a pacer controlled by the pH of the blood. A chronically implantable sensor determines the blood pH. The rate of an oscillator of an asynchronous pacer is controlled by the sensed pH. It has been shown that blood pH decreases during prolonged muscular exercise. Mauer et al. in U.S. Pat. No. 4,252,124 teach an improved pH sensor.

Wirtzfeld et al. in U.S. Pat. No. 4,202,339 teach a pacing system having the rate of an asynchronous oscillator controlled by the 0_2 level of the intracardiac venous blood. As with all known prior art, physiologically controlled pacers, Wirtzfeld et al. teach what is essentially an asychronous pacer as described by the above identified patent issued to Greatbatch, with an oscillator rate directly controlled by the measured parameter. As such, these devices are less than optimal for treating cases of partial heart block.

SUMMARY OF THE INVENTION

The present invention employs demand mode pacing with an escape interval that is determined by a measured physiological parameter. This results in a pacer system which can intermittently pace, upon demand, in hearts with partial block or sick sinus syndrome at a minimum rate that varies with physiological requirements. The preferred mode senses level of molecular oxygen within intracardiac venous blood. As the oxygen level decreases, the escape interval is shortened thus providing a higher minimum rate. Similarly, an increase in oxygen level causes a lengthened escape interval. Notice that, unlike prior art physiologically controlled pacers, the present invention treats partial heart block or sick sinus syndrome in the demand mode.

The present invention may be readily employed with sensors which measure other parameters, such as pH of blood, respiration rate, etc. Also, the present invention is readily utilized in both single chamber and two-chamber pacing modes.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic diagram of a typical prior art physiologically controlled pacing system.

FIG. 2 is a schematic diagram of a single chamber pacing system employing the present invention.

FIG. 3 is a schematic diagram of Demand Logic 106.

FIG. 4 is a schematic diagram of Sensor Processing 30.

FIG. 5 is a schematic diagram of the dual-chamber pacing system employing the present invention.

FIG. 6*a* is a table relating shift register position and corresponding minimum heart rate.

FIG. 6*b* is a table relating oxygen level to escape interval.

DETAILED DESCRIPTIONS OF THE PREFERRED EMBODIMENTS

The present invention is described herein in relation to the preferred modes of single and two-chamber pacing systems employing sensors measuring molecular oxygen level in intracardiac venous blood. Those of skill in the art, however, will be readily able to apply these teachings to devices using other pacing modes and measuring other physiologic parameters.

FIG. 1 is a schematic diagram of a typical prior art physiologically controlled pacing system. Sensor 12 is located within right ventricle 20 of heart 10. Sensor 12 may measure molecular oxygen level in the intracardiac blood as taught by Wirtzfeld et al., for example. Line 14 transmits the output of Sensor 12 to Sensor processing 30 of pulse generator 24. Sensor processing 30 transforms the sensed signal into a signal for controlling the rate of variable rate oscillator 28 via line 32. The output of variable rate oscillator 28 is thus a train of pulses having an interpulse period determined by the sensed parameter. Driver 26 amplifies this pulse train which is transferred to stimulating electrode 18 via conductor 16. Thus, right ventricle 20 is stimulated asynchro-

nously of atrium 22 at a rate determined by the level of oxygen sensed by Sensor 12.

FIG. 2 is a schematic diagram of a single chamber pacing system employing the present invention. The system employs a prior art sensor 12 located within right ventricle 20 of heart 10. A probe for measuring oxygen level as disclosed in the Wirtzfeld et al. patent is preferable. However, the reader should acquaint himself with the papers: "A Miniature Fiber Optic pH Sensor Suitable for In-Vivo Application," by Goldstein et al. of the National Institute of Health and "Fiber Optic pH Probe for Physiological Use," *Analytical Chemistry*, Vol. 52, pp 864–869 (1980) by Peterson et al. Though these papers describe devices for measuring the less desirable parameter of pH, the technique of indirect measuremeni they propose seems promising for chronically implantable oximetry sensors as well. Sensor processing 30 converts the analog signal received from sensor 12 via line 14 into digital form and transfers a digital escape interval control signal to demand logic 106 via line 32.

Line 104 transfers an intracardiac EKG signal from right ventricle 20 to sense amp 102. The operation of sense amp 102 is common in the art. Its purpose is to examine the intracardiac EKG signal received via line 104 and determine when a QRS complex of natural oriqin is sensed. The output of sense amp 102 via line 108 signifies that no artificial stimulation pulse should be generated for at least one complete escape interval, since a naturally paced contraction has just occurred. U.S. Pat. No. 3,478,746 issued to Greatbatch teaches the function and operation of such a sense amplifier.

Fixed rate oscillator 112 serves as an internal clock for demand logic 106. A rate of 60 hertz is chosen as sufficiently fast and yet conserving of power. Fixed rate oscillator 112 supplies a 60 hertz pulse train to demand logic 106 via line 110.

Demand logic 106 counts an escape interval having a period established by sensor processing 30 in multiples of 1/60 second. If a pulse is not received from sense amp 102 via line 108 during that escape interval, demand logic 106 transfers a pulse enable signal to driver 26 via line 34. If a pulse is received from sense amp 102, a naturally paced contraction has occurred and the escape interval is reset without transferring a pulse enable signal to driver 26 via line 34. The important feature is that the escape interval is not fixed but is a period determined by the signal received from sensor processing 30 via line 32 which is indicative of the current oxygen level in the intracardiac blood.

Driver 26 receives the pulse enable signal from demand logic 106 via line 34 and produces a stimulation pulse which is transferred to the tissue of right ventricle 20 by conductor 16 and electrode 18. Driver 26 is preferably a capacitive discharge circuit common in the art. The design of such a circuit may be found in commonly assigned U.S. Pat. No. 4,276,883 issued to McDonald et al.

FIG. 3 is a detailed schematic diagram of demand logic 106. The function of demand logic 106 is to count a period of time equivalent to the escape interval for the current level of oxygen in the intracardiac blood and generate a pulse enable signal if and only if no QRS complex was detected during that escape interval. Upon generation of a pulse enable or receipt of a QRS complex detection signal, the escape interval is reset to zero.

The clock signal is a 60 hertz pulse train received from fixed rate oscillator 112 via line 110 as explained above. The clock signal serves to sequence 30 bit shift register 156 and 38 bit shift register 158. These are constructed from common CMOS monolithic part types.

OR gate 150 outputs a start reset signal whenever a QRS detect signal is received from sense amp 102 via line 108 or a pulse enable signal is generated and transmitted to OR gate 150 via line 34*a*. One-shot 152, being a common part type forms the start reset signal into a clear signal suitable for clearing 30 bit shift register 156 and 38 bit shift register 158. The output of one-shot 152 supplies the clear signal via lines 168*a* and 168*b* to 30 bit shift register 156 and 38 bit shift register 158, respectively.

The clear signal generated by one-shot 152 is also transferred to delay 154 which delays the pulse sufficiently long to enable 30 bit shift register 156 and 38 bit shift register 158 to be cleared. The pulse width of the clear signal is a sufficient delay time. The output of delay 154 is transferred via line 170 to set the least significant bit (LSB) position of 30 bit shift register 156. The result is that 30 bit shift register 156 and 38 bit shift register 158 are both cleared at the occurrence of a sensed QRS complex or the generation of a stimulating pulse. The LSB is next set and shifted one bit position at each pulse of the clock signal (i.e., at 60 hertz). It is easily seen that the LSB requires 500 milliseconds to shift to the carry output of 30 bit shift register 156 from whence it is propogated via line 166 to the LSB position of 38 bit shift register 158. Again, it requires 1/60 second to shift to each succeeding bit position of 38 bit shift register 158.

It would take an additional 633 milliseconds for the set bit to shift the entire length of 38 bit shift register 158. This provides a total time of 1.133 seconds to shift the entire combined length of 30 bit shift register 156 and 38 bit shift register 158. The maximum escape interval for the system is therefore 1.133 seconds, which corresponds to a heart rate of 52.9 beats per minute.

The output of each of the 38 bit positions of 38 bit shift register 158 is supplied via cable 164 to 38×1 MUX 162. By selecting the desired one of the 38 bit positions any one of 38 different escape intervals may be provided between 500 milliseconds (corresponding to 120 beats per minute) and 1.133 milliseconds (corresponding to 52.9 beats per minutes) in 1/60 second intervals. Of course, the rate of the clock signal may be increased to achieve greater resolution if required. Similarly, the length of 38 bit shift register 158 may be changed and/or the length of 30 bit shift register 156 changed to change the range of selectable escape intervals.

Common monolithic CMOS parts are used to fabricate 38×1 MUX 162. A six bit input received from six bit latch 160 via line 161 selects one of the 38 bit positions of 38 bit shift register 158 and thus determines the escape interval. If the LSB entered into 30 bit shift register 156 reaches the selected one of the 38 bit positions of 38 bit shift register 158, 38×1 MUX 162 outputs the pulse enable signal via line 34. Referring again to FIG. 2, it is seen that this results in the output of a stimulating pulse by driver 26. To ensure a minimum rate based upon the maximum escape interval, the carry output of 38 bit shift register 158 may be "ORED" with line 34. This is an optional safety measure.

Referring again to FIG. 3, selection by 38×1 MUX 162 is made by the six bit contents of six bit latch 160 which simply holds the current escape interval selector as received from sensor processing 30. A single com-

mon monolithic CMOS part is available to implement six bit latch 160.

Two control signals are required by six bit latch 160 as received by cable 32a. A first one of these signals clears the contents of six bit latch 160 and a second one is delayed and enables the six bit quantity on cable 32b to be latched into six bit latch 160.

FIG. 4 is a detailed schematic view of sensor processing 30. The analog sensor information is received from sensor 12 via line 14. As in Wirtzfeld et al., this is simply a signal having a voltage that is proportional to the percentage of concentration of molecular oxygen in the intracardiac venous blood. Amp 172 processes the analog signal and scales it for input to six bit A/D 176 via line 182. The processed analog signal is converted by six bit A/D 176 into a digital signal which is transmitted via cable 32b to six bit latch 160. The data ready output signal is supplied via one conductor of cable 32a to clear six bit latch 160. The data ready signal is delayed by delay 178 and sent via the other conductor of cable 32a to enable the six bit data into six bit latch 160. Clock 174 supplies the convert signal to six bit A/D 176. Clock 174 may have a very low rate (i.e., a fraction of one hertz) as the measurable changes in blood oxygen level occur slowly relative to the conversion time of six bit A/D 176 and the resulting escape interval. Fixed rate oscillator 112 or a submultiple thereof may be substituted for clock 174, but the asynchrony of a separate clock 174 is probably not detrimental and requires fewer components.

FIG. 5 is an alternate embodiment of the present invention as incorporated in a two-chamber pacing system. The elements of sensor processing 30, sensor 12, electrode 18, demand logic 106 and fixed rate oscillator 112 are identical to the corresponding elements of the single chamber system and function as discussed above. Driver (v) 26 is also identical to the driver 26 of the single chamber system.

Sense amp 102 of the single chamber system is replaced by sense amp (p) 102a which is coupled via line 104a to an electrode in atrium 22. In this way sense amp 102a monitors the atrial activity rather than the ventricular activity monitored by sense amp 102 in the single chamber system (see also FIG. 2). Therefore, sense amp 102a (p) generates a p-wave sensed signal which is transferred to demand logic 106 via line 108, whenever atrium 22 is naturally paced. Sense amp (p) 102a is similar to sense amp 102 except for the enhanced sensitivity as is commmonly known in the art for p-wave sense amplifiers.

As with the single chamber system, demand logic 106 generates a pulse enable circuit whenever the escape interval period has been reached as explained above. However, in this embodiment, the escape interval is measured between p-waves rather than between r-waves. Therefore a delay is supplied by A-V delay 202 to simulate the normal atrial-to-ventricular propogation delay. This may be a fixed delay which is easily accomplished or may be a delay which is related to the pacing rate (i.e., the inverse of the escape interval) as is also known in the art.

Atrium 22 may also be artificially stimulated using driver (A) 204 and conductor 206. This option provides an effective therapy for combined intermittent sinus-atrial block, sick sinus syndrome, sinus bradycardia, and atrial-ventricular block. The optional driver (A) 204 improves hemodynamic performance by stimulating a synchronized atrial kick.

Other configurations can be readily constructed using the teachings found herein. For example, driver (V) 26 may be deleted with only driver (A) 204 in use. This configuration would readily treat intermittent sinus-atrial block or sick sinus syndrome in a patient having normal atrial-ventricular conduction.

FIG. 6a is a table showing the effective minimum heart rate in beats per minute corresponding to various selected bit positions of 30 bit shift register 156 and 38 bit shift register 158 (with the total cumulative number of bit positions shown). The maximum number of bit positions permitted by the embodiment of demand logic 106 shown in FIG. 3 is 68. However, the table of FIG. 6a is extended to 78 bit positions to show the effect of extending 38 bit shift register 158 to 48 bits.

FIG. 6b shows the relationship between a given level of molecular oxygen in the intracardiac venous blood and the output required of six bit A/D 176 to six bit latch 160. This result is obtained by adjusting the bias of amp 172 to provide a zero voltage input to six bit A/D 176 for an oxygen level of 60% of saturation. The gain of amp 172 is adjusted to drive six bit A/D 176 to approximately one-half of its maximum value for an oxygen level of 70% of saturation. As can be seen, therefore, a five bit A/D conversion is sufficient for the chosen system resolution. However, six bit devices are more commonly available. The total measured range of interest in oxygen level is between 60% and 70%. Because of the components chosen, this provides an escape interval range corresponding to 52.9 to 120 beats per minute. The system is self-limiting to remain within this range. The ideal relationship of saturation levels to escape interval can vary from patient to patient, and is preferrably programmable using an external device. Support may be readily found in the current literature to permit determination of other effective relationships.

What is claimed is:

1. A demand heart pacemaker for providing stimulating pulses to the heart at a predetermined rate in the absence of naturally occurring heartbeats comprising:
   - sensing means for sensing naturally occurring heart signals and generating a reset signal;
   - pulse generator means for generating stimulating pulses at a minimum pacing rate, including timing means for providing each stimulating pulse separated by an escape interval corresponding to the pacing rate and reset means responsive to a reset signal for resetting said timing means and restarting the escape interval;
   - means for measuring a physiological parameter indicative of the level of cardiac output demanded by the patient's body and for providing an escape interval modifying signal; and
   - means responsive to the escape interval modifying signal for adjusting the escape interval to provide pacing pulses on demand at a minimum rate correlated to the cardiac output requirements of the patient.

2. A demand heart pacemaker according to claim 1 wherein said adjusting means further comprises means for decreasing the escape interval.

3. A demand heart pacemaker according to claim 1 or 2 wherein said adjusting means further comprises means for increasing the escape interval

4. A demand heart pacemaker according to claim 1 wherein said physiological parameter is molecular oxygen level is venous blood

5. A demand heart pacemaker according to claim 1 wherein said predetermined electrical event comprises an R-wave.

6. A demand heart pacemaker according to claim 1 wherein said predetermined electrical event comprises a P-wave.

7. A demand heart pacemaker for providing stimulating pulses to the heart at a predetermined rate in the absence of naturally occurring heartbeats, comprising:

sensing means for sensing naturally occurring electrical heart signals and for generating a reset signal in response to sensing said naturally occurring heart signals;

pulse generator means for generating stimulating pulses at a minimum pacing rate, including timing means for providing each stimulating pulse at the termination of an escape interval corresponding to the pacing rate and reset means responsive to said reset signal for resetting said timing means and restarting said escape interval;

means for measuring a chemical parameter of venous blood indicative of the level of cardiac output demanded by the patient's body and for providing an escape interval modifying signal determined by the measurement of said chemical parameter; and

means responsive to the escape interval modifying signal for adjusting the escape interval to provide pacing pulses on demand at a minimum rate correlated to the cardiac output requirements of the patient.

* * * * *

EXHIBIT D

United States Patent [19]

Bornzin

[54] **RATE ADAPTIVE DEMAND PACEMAKER**

[75] Inventor: **Gene A. Bornzin**, Coon Rapids, Minn.

[73] Assignee: **Medtronic, Inc.**, Minneapolis, Minn.

[21] Appl. No.: **323,507**

[22] Filed: **Nov. 23, 1981**

[51] **Int. Cl.**³ **A61N 1/36**
[52] **U.S. Cl.** ..... **128/419 PG**
[58] **Field of Search** ..... 128/419 PG

[56] **References Cited**

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An article entitled "A New Pacemaker Autoregulating the Rate of Pacing in Relation to Metabolic Needs," by Cammilli, et al., published in the Proceedings of the 5th International Symposium, 1976 Tokyo.

Primary Examiner—William E. Kamm
Attorney, Agent, or Firm—Reed A. Duthler; John L. Rooney; Joseph F. Breimayer

[57] **ABSTRACT**

An implantable pacer having an effective stimulation rate which varies in response to a measured physiological parameter. Changes in the parameter to be measured must be related to physiologically required changes in heart rate. The level of oxygen within intracardiac or pulmonary artery venous blood is the preferred parameter. This parameter is measured by an oxygen sensor located on a transvenously implanted lead. As with normal demand pacers, a sensing electrode, also located on the lead, provides the pacer with an indication of whether a pacing pulse must be generated. The measured physiological parameter determines the escape interval for demand pacing. As such, a given minimum rate is determined for a given level of molecular oxygen in the intracardiac or pulmonary artery venous blood. The technique is readily employed in both ventricular and atrial-ventricular sequential modes.

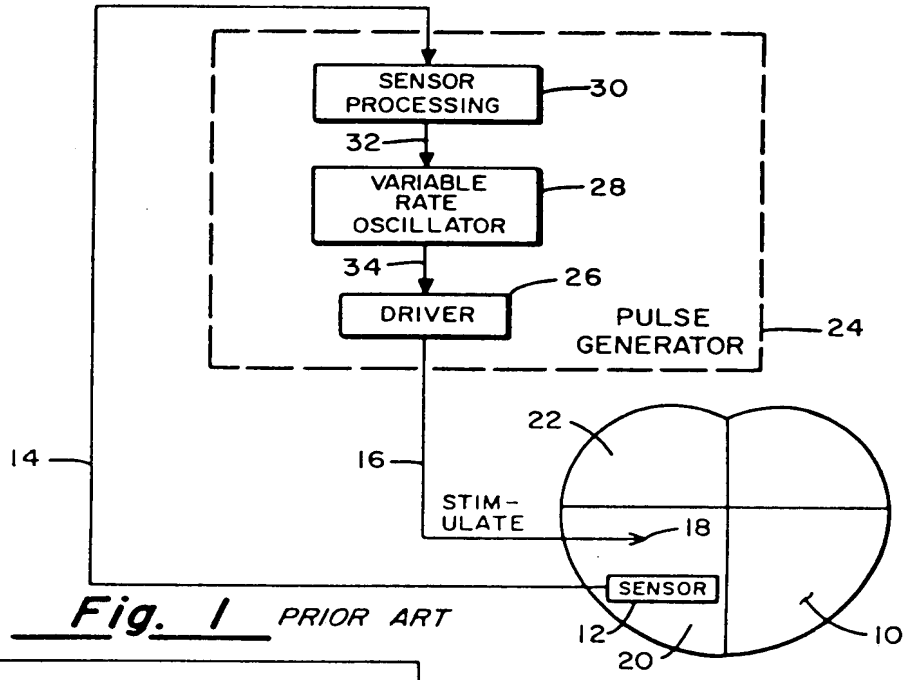

Fig. 1 PRIOR ART

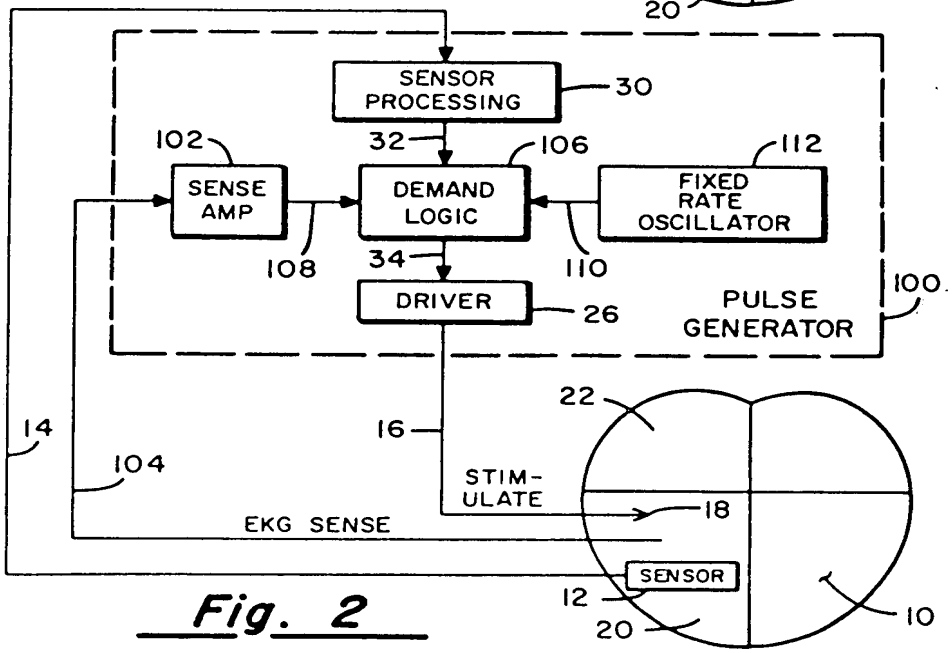

Fig. 2

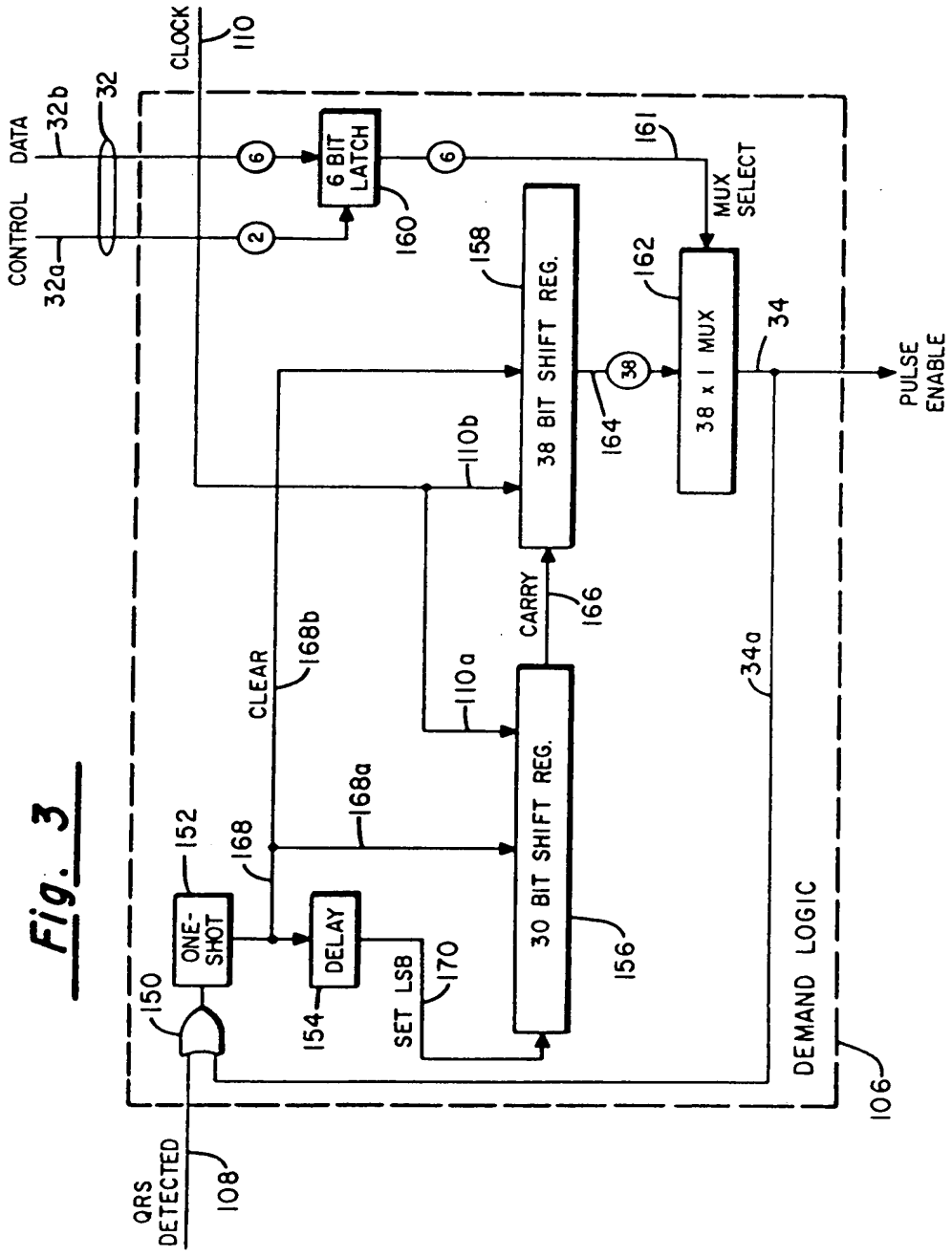
CLOCK
110
DATA
32b
32
CONTROL
32a
6
2
6 BIT LATCH
160
161
MUX SELECT
158
38 BIT SHIFT REG.
162
38 x 1 MUX
34
PULSE ENABLE
38
164
110b
CARRY
166
CLEAR
168b
110a
34a
168a
168
152
ONE-SHOT
DELAY
154
SET LSB
170
30 BIT SHIFT REG.
156
150
DEMAND LOGIC
106
QRS DETECTED
108

Fig. 3

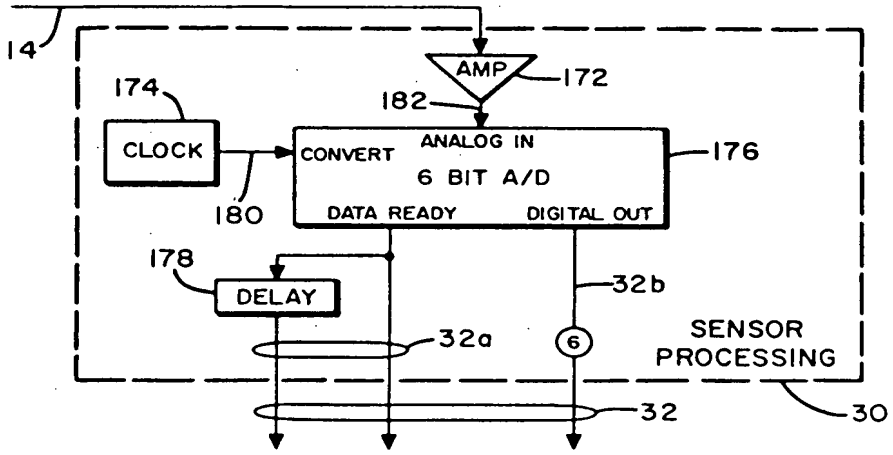
14
AMP
172
174
182
CLOCK
CONVERT
ANALOG IN
6 BIT A/D
176
180
DATA READY
DIGITAL OUT
178
DELAY
32b
32a
6
SENSOR
PROCESSING
32
30

Fig. 4

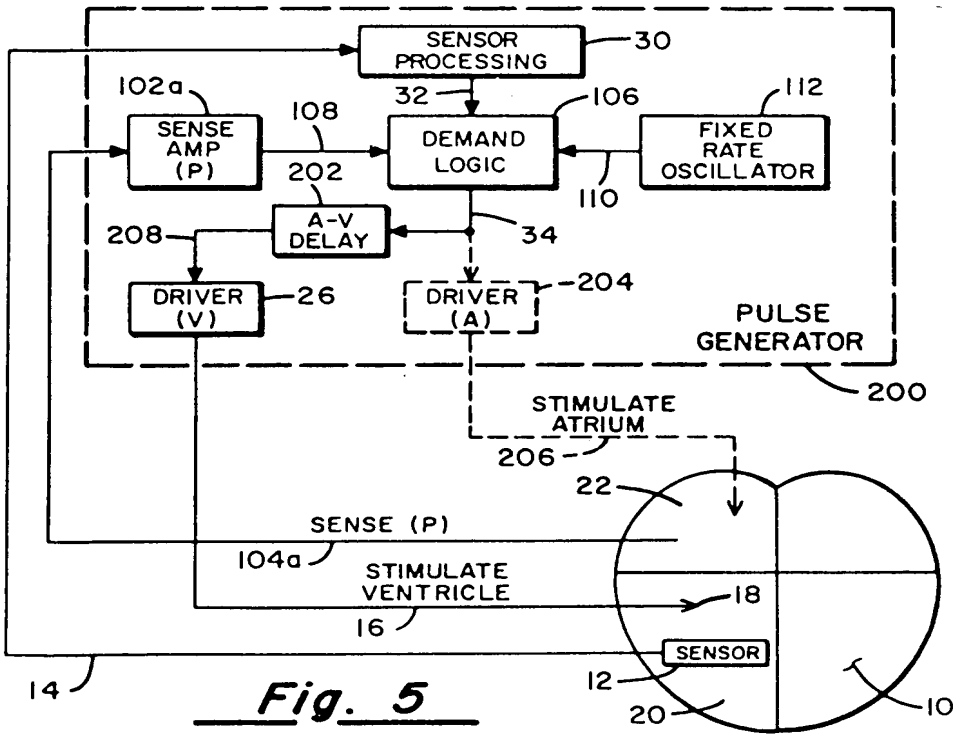
SENSOR
PROCESSING
30
102a
32
106
112
108
SENSE
AMP
(P)
DEMAND
LOGIC
FIXED
RATE
OSCILLATOR
202
110
208
A-V
DELAY
34
DRIVER
(V)
26
DRIVER
(A)
204
PULSE
GENERATOR
200
STIMULATE
ATRIUM
206
22
SENSE (P)
104a
STIMULATE
VENTRICLE
18
16
SENSOR
14
12
20
10

Fig. 5

BIT POSITION	RATE (BPM)
30	120
36	100
40	90
45	80
50	72
55	65.4
60	60
65	55.4
70	51.4
75	48
78	46

Fig. 6a

O_2 LEVEL (%)	BIT POSITION	6 BIT LATCH MSB LSB
70+	67	1 0 0 0 0 1
70	60	0 1 1 1 1 0
68	50	0 1 0 1 0 0
66	45	0 0 1 1 1 1
64	40	0 0 1 0 1 0
62	36	0 0 0 1 1 0
60	30	0 0 0 0 0 0

Fig. 6b

RATE ADAPTIVE DEMAND PACEMAKER

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to medical devices, and more specifically relates to implantable electronic devices for muscle stimulation.

2. Description of the Prior Art

The earliest implantable pacing systems operate asynchronously to normal physiologic functions. U.S. Pat. No. 3,057,356, issued to Greatbatch, teaches such a pacer which has a fixed rate oscillator coupled to an output driver circuit. Each cycle of the fixed rate oscillator causes generation of a stimulating pulse by the output driver circuit. Designs soon incorporated the demand feature which senses natural electrical activity in the heart and generates a stimulating pulse only if none is provided physiologically within a fixed escapement period. Demand mode pacers are now the most popular and probably outnumber all other types combined. Even though later improvements provide programmability of the escape interval, the effective pacing rate of such demand pacers is non-responsive to changes in physiological requirements.

There has been considerable work done in the area of physiologically controlled pacers. Most of these devices measure some parameter and adjust the period of the oscillator in response to changes therein. An early such device is taught by Cohen in U.S. Pat. No. 3,358,690. In this special case, however, the physiologic parameter measured is instantaneous blood pressure within the right atrium. This system will apparently work well for patients having complete atrial ventricular block with properly paced atria. The Cohen approach is not likely to be effective for sick sinus syndrome, sinus/atrial block, or similar disorders.

Later physiologically controlled pacer systems have been developed which have more general application and may be categorized by the parameter measured. Krasner et al. in U.S. Pat. No. 3,593,718 teaches sensing of mechanical activity within the thorax. It is assumed that changes in respiration rate are thereby sensed. The oscillator of the pacing system has its rate controlled by changes in this parameter. Dahl, in U.S. Pat. No. 4,140,132 teaches an improved implantable sensor for determining level of a patient's physical activity for rate-controlling a pacer as taught by Krasner et al.

Bozal Gonzalez in U.S. Pat. No. 4,201,219 teaches rate control of a pacer based upon neurological activity. Electrodes imbedded in the nervous system sense electrical activity. Somehow, the amount of this electrical activity is used to control the oscillator rate of an asynchronous pacer.

By far the most promising techniques appear to involve the sensing of certain chemical parameters of venous, often intracardiac blood. Alcidi in U.S. Pat. No. 4,009,721 teaches a pacer controlled by the pH of the blood. A chronically implantable sensor determines the blood pH. The rate of an oscillator of an asynchronous pacer is controlled by the sensed pH. It has been shown that blood pH decreases during prolonged muscular exercise. Mauer et al. in U.S. Pat. No. 4,252,124 teach an improved pH sensor.

Wirtzfeld et al. in U.S. Pat. No. 4,202,339 teach a pacing system having the rate of an asynchronous oscillator controlled by the 0_2 level of the intracardiac venous blood. As with all known prior art, physiologically

controlled pacers, Wirtzfeld et al. teach what is essentially an asychronous pacer as described by the above identified patent issued to Greatbatch, with an oscillator rate directly controlled by the measured parameter. As such, these devices are less than optimal for treating cases of partial heart block.

SUMMARY OF THE INVENTION

The present invention employs demand mode pacing with an escape interval that is determined by a measured physiological parameter. This results in a pacer system which can intermittently pace, upon demand, in hearts with partial block or sick sinus syndrome at a minimum rate that varies with physiological requirements. The preferred mode senses level of molecular oxygen within intracardiac venous blood. As the oxygen level decreases, the escape interval is shortened thus providing a higher minimum rate. Similarly, an increase in oxygen level causes a lengthened escape interval. Notice that, unlike prior art physiologically controlled pacers, the present invention treats partial heart block or sick sinus syndrome in the demand mode.

The present invention may be readily employed with sensors which measure other parameters, such as pH of blood, respiration rate, etc. Also, the present invention is readily utilized in both single chamber and two-chamber pacing modes.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic diagram of a typical prior art physiologically controlled pacing system.

FIG. 2 is a schematic diagram of a single chamber pacing system employing the present invention.

FIG. 3 is a schematic diagram of Demand Logic 106.

FIG. 4 is a schematic diagram of Sensor Processing 30.

FIG. 5 is a schematic diagram of the dual-chamber pacing system employing the present invention.

FIG. 6*a* is a table relating shift register position and corresponding minimum heart rate.

FIG. 6*b* is a table relating oxygen level to escape interval.

DETAILED DESCRIPTIONS OF THE PREFERRED EMBODIMENTS

The present invention is described herein in relation to the preferred modes of single and two-chamber pacing systems employing sensors measuring molecular oxygen level in intracardiac venous blood. Those of skill in the art, however, will be readily able to apply these teachings to devices using other pacing modes and measuring other physiologic parameters.

FIG. 1 is a schematic diagram of a typical prior art physiologically controlled pacing system. Sensor 12 is located within right ventricle 20 of heart 10. Sensor 12 may measure molecular oxygen level in the intracardiac blood as taught by Wirtzfeld et al., for example. Line 14 transmits the output of Sensor 12 to Sensor processing 30 of pulse generator 24. Sensor processing 30 transforms the sensed signal into a signal for controlling the rate of variable rate oscillator 28 via line 32. The output of variable rate oscillator 28 is thus a train of pulses having an interpulse period determined by the sensed parameter. Driver 26 amplifies this pulse train which is transferred to stimulating electrode 18 via conductor 16. Thus, right ventricle 20 is stimulated asynchro-

nously of atrium 22 at a rate determined by the level of oxygen sensed by Sensor 12.

FIG. 2 is a schematic diagram of a single chamber pacing system employing the present invention. The system employs a prior art sensor 12 located within right ventricle 20 of heart 10. A probe for measuring oxygen level as disclosed in the Wirtzfeld et al. patent is preferable. However, the reader should acquaint himself with the papers: "A Miniature Fiber Optic pH Sensor Suitable for In-Vivo Application," by Goldstein et al. of the National Institute of Health and "Fiber Optic pH Probe for Physiological Use," *Analytical Chemistry*, Vol. 52, pp 864–869 (1980) by Peterson et al. Though these papers describe devices for measuring the less desirable parameter of pH, the technique of indirect measuremeni they propose seems promising for chronically implantable oximetry sensors as well. Sensor processing 30 converts the analog signal received from sensor 12 via line 14 into digital form and transfers a digital escape interval control signal to demand logic 106 via line 32.

Line 104 transfers an intracardiac EKG signal from right ventricle 20 to sense amp 102. The operation of sense amp 102 is common in the art. Its purpose is to examine the intracardiac EKG signal received via line 104 and determine when a QRS complex of natural oriqin is sensed. The output of sense amp 102 via line 108 signifies that no artificial stimulation pulse should be generated for at least one complete escape interval, since a naturally paced contraction has just occurred. U.S. Pat. No. 3,478,746 issued to Greatbatch teaches the function and operation of such a sense amplifier.

Fixed rate oscillator 112 serves as an internal clock for demand logic 106. A rate of 60 hertz is chosen as sufficiently fast and yet conserving of power. Fixed rate oscillator 112 supplies a 60 hertz pulse train to demand logic 106 via line 110.

Demand logic 106 counts an escape interval having a period established by sensor processing 30 in multiples of 1/60 second. If a pulse is not received from sense amp 102 via line 108 during that escape interval, demand logic 106 transfers a pulse enable signal to driver 26 via line 34. If a pulse is received from sense amp 102, a naturally paced contraction has occurred and the escape interval is reset without transferring a pulse enable signal to driver 26 via line 34. The important feature is that the escape interval is not fixed but is a period determined by the signal received from sensor processing 30 via line 32 which is indicative of the current oxygen level in the intracardiac blood.

Driver 26 receives the pulse enable signal from demand logic 106 via line 34 and produces a stimulation pulse which is transferred to the tissue of right ventricle 20 by conductor 16 and electrode 18. Driver 26 is preferably a capacitive discharge circuit common in the art. The design of such a circuit may be found in commonly assigned U.S. Pat. No. 4,276,883 issued to McDonald et al.

FIG. 3 is a detailed schematic diagram of demand logic 106. The function of demand logic 106 is to count a period of time equivalent to the escape interval for the current level of oxygen in the intracardiac blood and generate a pulse enable signal if and only if no QRS complex was detected during that escape interval. Upon generation of a pulse enable or receipt of a QRS complex detection signal, the escape interval is reset to zero.

The clock signal is a 60 hertz pulse train received from fixed rate oscillator 112 via line 110 as explained

above. The clock signal serves to sequence 30 bit shift register **156** and 38 bit shift register **158**. These are constructed from common CMOS monolithic part types.

OR gate **150** outputs a start reset signal whenever a QRS detect signal is received from sense amp **102** via line **108** or a pulse enable signal is generated and transmitted to OR gate **150** via line **34***a*. One-shot **152**, being a common part type forms the start reset signal into a clear signal suitable for clearing 30 bit shift register **156** and 38 bit shift register **158**. The output of one-shot **152** supplies the clear signal via lines **168***a* and **168***b* to 30 bit shift register **156** and 38 bit shift register **158**, respectively.

The clear signal generated by one-shot **152** is also transferred to delay **154** which delays the pulse sufficiently long to enable 30 bit shift register **156** and 38 bit shift register **158** to be cleared. The pulse width of the clear signal is a sufficient delay time. The output of delay **154** is transferred via line **170** to set the least significant bit (LSB) position of 30 bit shift register **156**. The result is that 30 bit shift register **156** and 38 bit shift register **158** are both cleared at the occurrence of a sensed QRS complex or the generation of a stimulating pulse. The LSB is next set and shifted one bit position at each pulse of the clock signal (i.e., at 60 hertz). It is easily seen that the LSB requires 500 milliseconds to shift to the carry output of 30 bit shift register **156** from whence it is propogated via line **166** to the LSB position of 38 bit shift register **158**. Again, it requires 1/60 second to shift to each succeeding bit position of 38 bit shift register **158**.

It would take an additional 633 milliseconds for the set bit to shift the entire length of 38 bit shift register **158**. This provides a total time of 1.133 seconds to shift the entire combined length of 30 bit shift register **156** and 38 bit shift register **158**. The maximum escape interval for the system is therefore 1.133 seconds, which corresponds to a heart rate of 52.9 beats per minute.

The output of each of the 38 bit positions of 38 bit shift register **158** is supplied via cable **164** to 38×1 MUX **162**. By selecting the desired one of the 38 bit positions any one of 38 different escape intervals may be provided between 500 milliseconds (corresponding to 120 beats per minute) and 1.133 milliseconds (corresponding to 52.9 beats per minutes) in 1/60 second intervals. Of course, the rate of the clock signal may be increased to achieve greater resolution if required. Similarly, the length of 38 bit shift register **158** may be changed and/or the length of 30 bit shift register **156** changed to change the range of selectable escape intervals.

Common monolithic CMOS parts are used to fabricate 38×1 MUX **162**. A six bit input received from six bit latch **160** via line **161** selects one of the 38 bit positions of 38 bit shift register **158** and thus determines the escape interval. If the LSB entered into 30 bit shift register **156** reaches the selected one of the 38 bit positions of 38 bit shift register **158**, 38×1 MUX **162** outputs the pulse enable signal via line **34**. Referring again to FIG. **2**, it is seen that this results in the output of a stimulating pulse by driver **26**. To ensure a minimum rate based upon the maximum escape interval, the carry output of 38 bit shift register **158** may be "ORED" with line **34**. This is an optional safety measure.

Referring again to FIG. **3**, selection by 38×1 MUX **162** is made by the six bit contents of six bit latch **160** which simply holds the current escape interval selector as received from sensor processing **30**. A single com-

mon monolithic CMOS part is available to implement six bit latch **160**.

Two control signals are required by six bit latch **160** as received by cable **32***a*. A first one of these signals clears the contents of six bit latch **160** and a second one is delayed and enables the six bit quantity on cable **32***b* to be latched into six bit latch **160**.

FIG. **4** is a detailed schematic view of sensor processing **30**. The analog sensor information is received from sensor **12** via line **14**. As in Wirtzfeld et al., this is simply a signal having a voltage that is proportional to the percentage of concentration of molecular oxygen in the intracardiac venous blood. Amp **172** processes the analog signal and scales it for input to six bit A/D **176** via line **182**. The processed analog signal is converted by six bit A/D **176** into a digital signal which is transmitted via cable **32***b* to six bit latch **160**. The data ready output signal is supplied via one conductor of cable **32***a* to clear six bit latch **160**. The data ready signal is delayed by delay **178** and sent via the other conductor of cable **32***a* to enable the six bit data into six bit latch **160**. Clock **174** supplies the convert signal to six bit A/D **176**. Clock **174** may have a very low rate (i.e., a fraction of one hertz) as the measurable changes in blood oxygen level occur slowly relative to the conversion time of six bit A/D **176** and the resulting escape interval. Fixed rate oscillator **112** or a submultiple thereof may be substituted for clock **174**, but the asynchrony of a separate clock **174** is probably not detrimental and requires fewer components.

FIG. **5** is an alternate embodiment of the present invention as incorporated in a two-chamber pacing system. The elements of sensor processing **30**, sensor **12**, electrode **18**, demand logic **106** and fixed rate oscillator **112** are identical to the corresponding elements of the single chamber system and function as discussed above. Driver (v) **26** is also identical to the driver **26** of the single chamber system.

Sense amp **102** of the single chamber system is replaced by sense amp (p) **102***a* which is coupled via line **104***a* to an electrode in atrium **22**. In this way sense amp **102***a* monitors the atrial activity rather than the ventricular activity monitored by sense amp **102** in the single chamber system (see also FIG. **2**). Therefore, sense amp **102***a* (p) generates a p-wave sensed signal which is transferred to demand logic **106** via line **108**, whenever atrium **22** is naturally paced. Sense amp (p) **102***a* is similar to sense amp **102** except for the enhanced sensitivity as is commmonly known in the art for p-wave sense amplifiers.

As with the single chamber system, demand logic **106** generates a pulse enable circuit whenever the escape interval period has been reached as explained above. However, in this embodiment, the escape interval is measured between p-waves rather than between r-waves. Therefore a delay is supplied by A-V delay **202** to simulate the normal atrial-to-ventricular propogation delay. This may be a fixed delay which is easily accomplished or may be a delay which is related to the pacing rate (i.e., the inverse of the escape interval) as is also known in the art.

Atrium **22** may also be artificially stimulated using driver (A) **204** and conductor **206**. This option provides an effective therapy for combined intermittent sinus-atrial block, sick sinus syndrome, sinus bradycardia, and atrial-ventricular block. The optional driver (A) **204** improves hemodynamic performance by stimulating a synchronized atrial kick.

Other configurations can be readily constructed using the teachings found herein. For example, driver (V) **26** may be deleted with only driver (A) **204** in use. This configuration would readily treat intermittent sinus-atrial block or sick sinus syndrome in a patient having normal atrial-ventricular conduction.

FIG. **6***a* is a table showing the effective minimum heart rate in beats per minute corresponding to various selected bit positions of 30 bit shift register **156** and 38 bit shift register **158** (with the total cumulative number of bit positions shown). The maximum number of bit positions permitted by the embodiment of demand logic **106** shown in FIG. **3** is 68. However, the table of FIG. **6***a* is extended to 78 bit positions to show the effect of extending 38 bit shift register **158** to 48 bits.

FIG. **6***b* shows the relationship between a given level of molecular oxygen in the intracardiac venous blood and the output required of six bit A/D **176** to six bit latch **160**. This result is obtained by adjusting the bias of amp **172** to provide a zero voltage input to six bit A/D **176** for an oxygen level of 60% of saturation. The gain of amp **172** is adjusted to drive six bit A/D **176** to approximately one-half of its maximum value for an oxygen level of 70% of saturation. As can be seen, therefore, a five bit A/D conversion is sufficient for the chosen system resolution. However, six bit devices are more commonly available. The total measured range of interest in oxygen level is between 60% and 70%. Because of the components chosen, this provides an escape interval range corresponding to 52.9 to 120 beats per minute. The system is self-limiting to remain within this range. The ideal relationship of saturation levels to escape interval can vary from patient to patient, and is preferrably programmable using an external device. Support may be readily found in the current literature to permit determination of other effective relationships.

What is claimed is:

1. A demand heart pacemaker for providing stimulating pulses to the heart at a predetermined rate in the absence of naturally occurring heartbeats comprising:

sensing means for sensing naturally occurring heart signals and generating a reset signal;

pulse generator means for generating stimulating pulses at a minimum pacing rate, including timing means for providing each stimulating pulse separated by an escape interval corresponding to the pacing rate and reset means responsive to a reset signal for resetting said timing means and restarting the escape interval;

means for measuring a physiological parameter indicative of the level of cardiac output demanded by the patient's body and for providing an escape interval modifying signal; and

means responsive to the escape interval modifying signal for adjusting the escape interval to provide pacing pulses on demand at a minimum rate correlated to the cardiac output requirements of the patient.

2. A demand heart pacemaker according to claim **1** wherein said adjusting means further comprises means for decreasing the escape interval.

3. A demand heart pacemaker according to claim **1** or **2** wherein said adjusting means further comprises means for increasing the escape interval.

4. A demand heart pacemaker according to claim **1** wherein said physiological parameter is molecular oxygen level is venous blood.

5. A demand heart pacemaker according to claim 1 wherein said predetermined electrical event comprises an R-wave.

6. A demand heart pacemaker according to claim 1 wherein said predetermined electrical event comprises a P-wave.

7. A demand heart pacemaker for providing stimulating pulses to the heart at a predetermined rate in the absence of naturally occurring heartbeats, comprising:

sensing means for sensing naturally occurring electrical heart signals and for generating a reset signal in response to sensing said naturally occurring heart signals;

pulse generator means for generating stimulating pulses at a minimum pacing rate, including timing means for providing each stimulating pulse at the

termination of an escape interval corresponding to the pacing rate and reset means responsive to said reset signal for resetting said timing means and restarting said escape interval;

means for measuring a chemical parameter of venous blood indicative of the level of cardiac output demanded by the patient's body and for providing an escape interval modifying signal determined by the measurement of said chemical parameter; and

means responsive to the escape interval modifying signal for adjusting the escape interval to provide pacing pulses on demand at a minimum rate correlated to the cardiac output requirements of the patient.

* * * * *

EXHIBIT E

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

NOV 17 1983

RECEIVED

NOV 22 1983

Mr. Martin E. Kienitz
Product Regulation Manager
Medtronic, Inc.
3055 Old Highway Eight
P.O. Box 1453
Minneapolis, Minnesota 55440

Re: IDE Number G830107/A1
Medtronic Model 2447/2448
Pulse Generators
Dated: October 7, 1983
Received: October 11, 1983

Dear Mr. Kienitz:

FDA has reviewed the amendment to your investigational device exemption (IDE) application. You have corrected the deficiencies listed in our September 1, 1983 letter. Therefore, your application is approved and you may conduct the investigation at the two institutions listed in the attachment immediately after (1) institutional review board (IRB) approval is obtained and (2) FDA has received certification of that IRB approval. You may consider that FDA has received certification of IRB approval as of the date the certification is mailed or hand delivered to FDA.

Thirty pulse generators may be implanted by a maximum of ten investigators under the intensive phase of your protocol. No more than an additional 30 pulse generators implanted by an additional 10 investigators are approved for the general phase of the study, provided these patients receive the pre-implant screening specified in the intensive phase.

When investigators are added to the study, the following information must be submitted:

1. the name and address of the investigator at the new institution;
2. the name, address and chairperson of the IRB;
3. certification of any action taken by the IRB regarding the investigation; and
4. a current list of all participating investigators including the name of the institution and date of IRB approval, and a notation of any deleted institutions/investigators.

The submission of this information will serve in lieu of the required 6 month current investigator list when submitted with the request for additional investigators.

You must fulfill all sponsor responsibilities for an investigation of a significant risk device, as described in Subparts C and G of the IDE regulation. In particular, you are required to submit a progress report to FDA and all reviewing IRBs on at least a yearly basis and you are required to submit a current list of the names and addresses of all

investigators participating in the investigation to FDA at 6-month intervals. In accordance with Section 812.35(a), any change in the investigation which may affect the scientific soundness of the investigation or the rights, safety or welfare of the subjects must be submitted to and approved by FDA as a supplemental IDE application for any such change, and approved by the IRB for any change involving the rights, safety or welfare of the subjects. A supplemental IDE application is also required for the addition of new institutions in accordance with Section 812.35(b).

FDA approval of your application does not imply that this investigation will develop sufficient safety and effectiveness data to ensure FDA approval of a premarket approval application (PMA) for this device. You may obtain a guideline for the preparation of a PMA from the Office of Device Evaluation (HFK-402), 8757 Georgia Avenue, Silver Spring, Maryland 20910, or by calling (301) 427-7445.

Future correspondence concerning this application should be identified as an IDE supplement with the IDE number above and should be submitted, in triplicate, to:

Food and Drug Administration
National Center for Devices
and Radiological Health
Document Control Center (HFK-20)
8757 Georgia Avenue
Silver Spring, Maryland 20910

If you have any questions, please call the IDE Staff at (301) 427-8162 or Mr. Donald Dahms at (301) 427-7559.

Sincerely yours,

Robert G. Britain
Associate Director for
Device Evaluation
Office of Medical Devices
National Center for Devices
and Radiological Health

Attachment

EXHIBIT F

Medtronic

Medtronic, Inc.
3055 Old Highway Eight
P.O. Box 1453
Minneapolis, MN 55440 USA
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598

August 3, 1983

Food and Drug Administration
Office of Medical Devices (HFK-20)
8757 Georgia Avenue
Silver Spring, MD 20910

RE: Investigational Device Exemption
(IDE) Application

Gentlemen:

This application is submitted in triplicate in accordance with 21 59, Part 812, Investigational Device Exemption Regulation.

This submission contains contains confidential commercial and trade secret information and we respectfully request that the information be given maximum protection provided by law. If further information is required, please contact the undersigned.

Sincerely,

MEDTRONIC, INC.

Martin E. Kienitz

Martin E. Kienitz
Product Regulation Manager

Charles H Swanson

Charles H. Swanson, Ph. D.
Director, PSG Regulatory Affairs
(612) 574-3409

cvs
Att.

IDE APPLICATION

FOR

MEDTRONIC® MODEL 2447/2448 PULSE GENERATORS

Submitted by Medtronic, Inc.

August 3, 1983

Medtronic submits this Application for Investigational Device Exemption (IDE) under Section 812.20(a) for clinical investigation of the Model 2447/2448 pulse generators. This Application contains all information required under Section 812.20(b). With this Application, Medtronic requests exemption from all sections of the Federal Food, Drug and Cosmetic Act from which an investigational device may be exempted under Section 520(g) of the Act.

TABLE OF CONTENTS

REPORT OF PRIOR INVESTIGATIONS

FOR

MODEL 2447/2448 PULSE GENERATORS

INVESTIGATIONAL PLAN

FOR

MODELS 2447/2448 ACTIVITRAX™
ACTIVITY DETECTING PULSE GENERATOR

AUGUST, 1983

MEDTRONIC, INC.

David Wenell
Study Monitor
Clinical Evaluation Manager

Peter A. Chevalier, Ph.D.
Director, Clinical Evaluation Dept.

TECHNICAL MANUAL

THE ACTIVITRAX™ ACTIVITY DETECTING PULSE GENERATOR MODELS 2447 AND 2448

CLINICAL VERSION

CAUTION: Investigational Device. Limited by Federal Law to investigational use.

JULY 1983
Part Number: 176460-001
MC Number: 830309

EXHIBIT

Medtronic

Medtronic, Inc.
3055 Old Highway Eight
P.O. Box 1453
Minneapolis, MN 55440 USA
Telephone: (612) 574-4000
Cable: Medtronic Telex: 29-0598

July 19, 1985

Center for Devices and Radiological Health
Food and Drug Administration
Document Mail Center (HFZ-401)
8757 Georgia Avenue
Silver Spring, MD 20910

RE: Premarket Approval Application

Gentlemen:

Attached is a Premarket Approval Application for the Activitrax™ Models 8400/8402/8403 Activity Detecting Responsive Rate Pulse Generators manufactured by Medtronic, Inc.

Medtronic has reviewed the Models 8400/8402/8403 clinical results and proposed labeling with Models 8400/8402/8403 clinical investigators. Each investigator was provided with a draft of Section VI of the attached PMA and a copy of the proposed Models 8400/8402/8403 technical manual. On July 12, 1985 a meeting of investigators was held in Minneapolis.

The discussion during the meeting centered on the Activitrax clinical study objectives and results. Specifically, this included the following:

- Performance of the responsive rate pacing features of the Activitrax pulse generators,
- Device operation relative to activity pacing,
- Whether the labeling is adequate to describe device operation and the associated indications, contraindications, warnings, and precautions.

At the conclusion of the investigator meeting, the investigators unanimously agreed that there were no safety concerns and that adequate instructions for use are provided in the technical manual.

This application is submitted in accordance with Section 515(c) of the Federal Food, Drug and Cosmetic Act and has

been prepared according to the most recent FDA guidelines for Premarket Approval Applications. This application is in 8 volumes: Volume I (12 copies), Volume II (12 copies), Volume III (12 copies), Volume IV (5 copies), Volume V (1 copy), Volume VI (1 copy), Volume VII (1 copy), Volume VIII (1 copy).

This application contains confidential commercial and trade secret information. We respectfully request that you provide this information the maximum protection allowable by law.

If you require further information, please contact the undersigned.

Sincerely,

MEDTRONIC, INC.

Timothy J. Johnson

Timothy J. Johnson
Product Regulation Manager

Charles H Swanson

Charles H. Swanson, Ph.D.
Director, PSG Regulatory Affairs

cvs
Atts.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

OCT 31 1985

RECEIVED

NOV 05 1985

Mr. Timothy J. Johnson
Product Regulation Manager
Medtronic, Inc.
P.O. Box 1453
Minneapolis, Minnesota 55440

Re: P850051
Activitrax™ Models 8400, 8402 and 8403 Pulse Generator; Model 9710 Programmer; and Model 9721 Module
Filed: July 19, 1985

Dear Mr. Johnson:

FDA has completed an initial review of the above referenced premarket approval application (PMA). FDA has determined that your application is administratively acceptable and therefore, suitable for filing. The filing date is July 19, 1985, which is the date of receipt of the PMA.

The following deficiencies were noted in this initial review.

1. An explanation of the statistical models, assumptions, type of effect, and working data used in the analysis of variance is needed.

2. The statistical significance of the clinical testing results and their interpretation must be presented.

3. The manufacturing and quality control screen testing procedures which are performed at the component, module, and final assembly levels must be described.

4. The method of determining the "use before date" must be described.

5. The statistical analysis of the battery discharge data to verify the labeled replacement period must be included.

The PMA will now undergo scientific and compliance review. You may receive further inquiries from FDA reviewers. The PMA cannot be approved until FDA has determined that the manufacturing facilities, methods, and controls comply with applicable device Good Manufacturing Practice Regulations (21 CFR Part 820). Notify FDA in the form of a PMA amendment, of the earliest date your manufacturing facility is prepared or set up for production of the device so that an FDA inspection may be scheduled.

Submit 12 copies of all correspondence regarding this PMA, to be designated as PMA amendments, to the Food and Drug Administration, Center for Devices and Radiological Health, PMA Document Mail Center (HFZ-401), 8757 Georgia Avenue, Silver Spring, Maryland 20910. The above PMA number shall be referenced in all further correspondence to expedite processing.

If you have any questions concerning the status of the application, please contact Donald F. Dahms at (301) 427-7594.

Sincerely yours,

Charles H. Kyper

Charles H. Kyper
Director, PMA Staff
Office of Device Evaluation
Center for Devices and
Radiological Health

EXHIBIT

#017

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

RECEIVED

JUN 13 1986

Food and Drug Administration
8757 Georgia Avenue
Silver Spring MD 20910

JUN 10 1986

Mr. Timothy J. Johnson
Product Regulation Manager
Medtronic, Inc.
3055 Old Highway Eight
P.O. Box 1453
Minneapolis, Minnesota 55440

Re: P850051
Activitrax™ Models 8400, 8402 and 8403 Pulse Generator and Model 9710 Programmer with the Model 9725 MemoryMod™ Program Module
Filed: July 19, 1985
Amended: November 22 and December 16, 1985; and January 9, March 6, April 30, 1986, and May 30, 1986

Dear Mr. Johnson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the above referenced device system indicated for cardiac pacing. The PMA is approved subject to the conditions described below and in the "Conditions of Approval for Pulse Generators and Programmers" (enclosed). The approval for the Model 9710 Programmer with the Model 9725 MemoryMod™ Program Module includes only those pulse generators listed in Attachment A. You may begin production and marketing of the device upon receipt of this letter.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. In addition, the notice will state that a copy of all approved labeling (which may be a draft of the final labeling) is available for public inspection at the CDRH. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug and Cosmetic Act (act).

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act.

All stated requirements are subject to change upon publication of a final premarket approval procedural regulation. Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You shall submit all required documents in triplicate to the Food and Drug Administration, Center for Devices and Radiological Health, PMA Document Mail Center (HFZ-401), 8757 Georgia Avenue, Silver Spring, Maryland 20910. You shall refer to the above PMA number in all further correspondence to expedite processing.

If you have any questions concerning this approval order, please contact Donald F. Dahms at (301) 427-7594.

Sincerely yours,

Kshitij Mohan

Kshitij Mohan, Ph.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

Attachment A

PULSE GENERATORS PROGRAMMABLE BY THE MODEL 9710 PROGRAMMER/9725 MEMORYMOD™ PROGRAM MODULE

Family	Applicable Models	
Spectrax®	5940, 5940LP, 5941	(Spectrax S™)
	5984, 5984LP, 5985	(Spectrax SX™)
	5976, 5977	(Spectrax SX™-HT)
	8420, 8422, 8423	(Spectrax SXT™)
Classix™	8436, 8437, 8438	
Basix™	8432, 8433, 8434	
Byrel-SX™	5993-SX	
Pasys™	8320, 8322, 8329	
Models	8316, 8317, 8318	
Enertrax®	7100,	
	7100E	
Activitrax™	8400, 8402, 8403	
Symbios®	7005, 7005C, 7006	
Models	7001, 7002	
Versatrax®	7000,	
	7000A	(Versatrax II)

Approved Labeling. As soon as possible, and before commercial distribution of your device, submit two copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the Food and Drug Administration (FDA), Center for Devices and Radiological Health, PMA Document Mail Center (HFZ-401), 8757 Georgia Avenue, Silver Spring, Maryland 20910.

Advertisement. No advertisement for this device shall recommend or imply that the device may be used for any use that is not mentioned in the approved labeling for the device. All written promotional material shall include a brief statement of the intended uses of the device and relevent warnings, precautions, side effects, and contraindictions.

Premarket Approval Application (PMA) Supplement. Before making any change that could affect the safety or effectiveness of the device, submit a PMA supplement for review and approval by Center for Devices and Radiological Health (CDRH). Such changes may include, but are not limited to:

(1) new indications for use;

(2) labeling changes;

(3) changes in existing manufacturing facilities, methods or quality control procedures;

(4) the use of a different facility or establishment to manufacture, process, or package the device;

(5) changes in sterilization procedures;

(6) changes in packaging;

(7) changes in the performance or design specification, circuits, parts, components, accessories, ingredients, or physical layout of the device; and

(8) extension of the expiration date of the device based on data obtained under a new or revised testing protocol that has not been approved by CDRH. If the protocol has been approved, the change shall be submitted along with the supporting data in the next periodic report required in the PMA approval order. An approved protocol is one included in FDA guidelines applicable to the device or in a PMA submission for the device for which the approval order granted the expiration dating requested by you. Otherwise, you must submit and obtain CDRH approval of a PMA supplement for an expiration dating protocol.

Changes described below that enhance the safety of the device or safety in the use of the device may be placed into effect before your receipt of a written FDA order approving the PMA supplement provided that:

(1) the PMA supplement and its mailing cover are plainly marked "Special PMA Supplement - Changes Being Effected";

(2) the PMA supplement provides a full explanation of the basis for

(4) detailed information concerning all explants reported to or known to the applicant, whether or not the pacemakers were returned for analysis, and the reasons for the explants;

(5) detailed information concerning all deaths reported to the company or known to the applicant, and the reasons for the patient deaths;

(6) the results of analyses performed on all returned programmers and pacemakers, whether implanted or not implanted;

(7) reports of all adverse experiences, whether identified as confirmed or unconfirmed; and

(8) detailed information concerning all failed pacemakers, and programmers and the reason for each failure.

Adverse Reaction and Device Defect Reporting. You shall submit 3 copies of a written report to the Food and Drug Administraiton, Center for Devices and Radiological Health (CDRH), 8757 Georgia Avenue, Silver Spring, Maryland 20910 within 10 days after you receive or have knowledge of information about:

(1) a mixup of the device or its labeling with another article;

(2) any significant chemical, physical, or other change or deterioration in the device, or any failure of one or more of the the devices to meet the specifications established in the application;

(3) any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device; and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occuring with unexpected severity or frequency.

Reporting under the Medical Device Reporting (MDR) Regulation. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise become aware of information that reasonably suggests that one of its marketed devices (1) may have caused or contributed to a death or serious injury or (2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to reoccur.

The conditions of approval accompanying PMA approval orders may require that the same events subject to reporting under the MDR Regulation must also be included in periodic reports to the PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the conditions of approval for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following offices:

(3) the applicant has received acknowledgement of FDA receipt of the PMA supplement;

(4) the PMA supplement specifically identifies the date that such changes are being effected; and

(5) the changes are among the following:

(a) labeling changes that add or strengthen a contraindication, warning, precaution, or adverse reaction or effect;

(b) labeling changes that add or strengthen an instruction that is intended to enhance the safe use of the device;

(c) labeling changes that delete misleading, false, or unsupported indications; or

(d) changes in the manufacturing process or quality controls that add a new specification or test method, or otherwise provide additional assurance of purity, identity, strength or reliability of the device.

You need submit only three (3) copies of a PMA supplement and include only information relevant to the proposed or effected changes in the device. The submission shall include a separate section that identifies all changes for which approval is being requested. You shall submit additional copies and additional information if requested by CDRH.

FDA may, as experience permits, issue guidelines listing specific types of changes that do not require FDA approval before implementation.

Post-Approval Reports. Continued approval of your device is contingent upon the submission of 2 copies of post-approval reports to the Food and Drug Administration, Center for Devices and Radiological Health, PMA Document Mail Center (HFZ-401), 8757 Georgia Avenue, Silver Spring, Maryland 20910 at intervals of 1 year from the date of this letter. The required contents of these reports will be described in the final order for the premarket approval procedural regulation which will be published in the FEDERAL REGISTER in the future. Until this regulation is published in final form, each periodic report shall consist of information that previously has not been submitted as part of a PMA supplement and which you have obtained since the last post-approval report or since receipt of this letter, whichever is later:

(1) a bibliography and summary of reports in the scientific literature involving the device and unpublished reports of in vitro, animal and clinical experience studies, investigations, and tests conducted by, reported to, or reasonably available to you involving the device or a related device--if, after reviewing the bibliography and summary, CDRH concludes that it needs a copy of the published and unpublished reports, CDRH will notify you that copies of such reports shall be submitted;

(2) written promotional material; and

(3) a description of changes made in the device not previously submitted in a PMA supplement.

Device Monitoring Branch (HFZ-343)
Center for Devices and Radiological Health
Food and Drug Administration
8757 Georgia Avenue
Silver Spring, Maryland 20910
Telephone (301) 427-7500

Copies of the MDR Regulation and a FDA publication entitled, "An Overview of the Medical Device Reporting Regulation", are available by written request to the above address or by telephoning (301) 427-8100.

Note: All conditions of approval are subject to change upon publication of the final order for the premarket approval procedural regulation.

EXHIBIT I

Chronological History of Activitrax Regulatory Activities

August 3, 1983	Activitrax Model 2447/2448 IDE submitted to FDA
September 1, 1983	FDA responds with an IDE deficiency letter
October 7, 1983	Medtronic submits IDE supplement to respond to deficiencies
November 17, 1983	IDE approved - clinical study begins
February 1, 1984	IDE supplement to add Model 2448-LP
February 28, 1984	FDA approves Model 2448-LP
March 29, 1984	IDE supplement to raise investigator limit
April 4, 1984	IDE supplement to alter device parameters
May 7, 1984	FDA disapproves change to investigator limit
May 21, 1984	FDA approves device change
May 24, 1984	IDE supplement to add new programmer, modify a component, and change model numbers to 8400,8402
June 22, 1984	IDE supplement to raise investigator limit
July 3, 1984	FDA approves May 24, 1984 submission
July 30, 1984	FDA approves investigator limit
October 17, 1984	IDE supplement to add Model 8403
November 20, 1984	IDE supplement requests device limit apply to the post May, 1984 device configuration only
December 7, 1984	FDA approves Model 8403 - IDE waiver granted
December 21, 1984	FDA approves device limit on latest configuration only
January 31, 1984	IDE supplement to provide the study progress report

February 6, 1985	IDE supplement for device changes to improve productibility
February 25, 1985	FDA disapproves February 6 supplement - deficiencies
March 26, 1985	IDE supplement to provide clinical data and to request study expansion
April 1, 1985	IDE supplement responding to February 25 deficiencies
April 25, 1985	FDA approves February 6 IDE supplement
April 26, 1985	FDA approves March 26 IDE supplement
May 29, 1985	Clinical data base closed for PMAA submission
July 19, 1985	PMAA submitted to FDA
October 15, 1985	Clinical data base closed for PMAA update
October 15, 1985	IDE supplement - minor device modification
October 31, 1985	FDA letter accepting PMAA for filing
November 13, 1985	IDE supplement requesting expanded device limit
November 14, 1985	FDA approves October 15 IDE supplement
November 20, 1985	PMAA amendment requesting facility inspection
November 21-22, 1985	Labeling review meeting with FDA
December 5, 1985	IDE supplement to support the requested expanded device limit
December 10, 1985	Device demonstration at FDA
December 13, 1985	FDA approves November 13 IDE supplement
December 13, 1985	PMAA amendment - updated PMAA
January 8, 1986	PMAA amendment - alternate programmer software cartridge added